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From Adaptive to Maladaptive Fear: Heterogeneity in Threat and Safety Learning across Response Systems in a Representative Sample

Femke J. Gazendam*^{1,2}, Angelos-Miltiadis Kryptos*³, Jan H. Kamphuis¹, Andries R. van der Leij^{2,4},
Hilde M. H. Huizenga^{2,5}, Annemarie Eigenhuis¹⁺, Merel Kindt^{1,2}

¹Department of Clinical Psychology

²Amsterdam Brain and Cognition

³KU Leuven & Utrecht University

⁴Department of Brain and Cognition

⁵Department of Developmental Psychology

University of Amsterdam

Nieuwe Achtergracht 129, 1018 WT Amsterdam, The Netherlands

³Department of Clinical Psychology,

Utrecht University

Heidelberglaan 1, 3584 CS Utrecht, The Netherlands,

+ Deceased

*Shared first authorship

Corresponding Author: Femke J. Gazendam, University of Amsterdam, Faculty of Social and Behavioral Sciences, Department of Clinical Psychology, Nieuwe Achtergracht 129, 1018 WT Amsterdam, The Netherlands, E-mail: Femke.Gazendam@gmail.com, Telephone Number: (+31) 20 525 6810, Fax Number: (+31) 20 525 6971.

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Abstract

Individual differences in fear learning are a crucial prerequisite for the translational value of the fear-conditioning model. In a representative sample ($N=936$), we used latent class growth models to detect individual differences in associative fear learning. For a series of subsequent test phases varying in ambiguity (i.e., acquisition, extinction, generalization, reinstatement, and re-extinction), conditioned responding was assessed on three response domains (i.e., subjective distress, startle responding, and

skin conductance). We also associated fear learning across the different test phases and response domains with selected personality traits related to risk and resilience for anxiety, namely Harm Avoidance, Stress Reaction, and Wellbeing (MPQ; Tellegen & Waller, 2008). Heterogeneity in fear learning was evident, with fit indices suggesting subgroups for each outcome measure. Identified subgroups showed adaptive, maladaptive, or limited-responding patterns. For subjective distress, fear and safety learning was more maladaptive in the subgroups high on Harm Avoidance, while more adaptive learning was observed in subgroups with medium Harm Avoidance and the limited- or non-responders were lowest in Harm Avoidance. Distress subgroups did not differ in Stress Reaction or Wellbeing. Startle and SCR subgroups did not differ on selected personality traits. The heterogeneity in fear-learning patterns resembled risk and resilient anxiety development observed in real life, which supports the associative fear-learning paradigm as a useful translational model for pathological fear development.

Keywords: associative fear learning, fear conditioning, anxiety, individual differences, anxiety vulnerability, translational research

Introduction

The extensive work on the associative fear-learning model has been highly valuable for revealing the general principles of learning and memory (LeDoux, 2014; Milad & Quirk, 2012). The study of associative learning is typically based on the laboratory paradigm of Pavlovian fear conditioning, during which aversive stimuli (e.g., shocks; Unconditioned Stimulus or UCS) are coupled with innocuous cues (e.g., pictures of faces; Conditioned Stimulus or CS) to elicit learned fear behaviour in response to the originally neutral stimulus. Along the tradition of basic science on fear conditioning, there has also been a long-standing interest in the clinical science of fear learning and memory (Craske, Hermans, & Vansteenwegen, 2006; Kindt, 2014). It has been argued that learned fear responses present in anxiety disorders follow similar principles of associative fear learning, when a neutral stimulus (e.g., crowded bus) becomes associated with an emotional event (e.g., panic) (Bouton, 2007; Mineka & Zinbarg, 2006). Despite the parallel interest in the neurobiological, cognitive, and behavioural underpinnings of maladaptive fear learning and memory, the extent to which individual

differences manifest in the fear-conditioning paradigm remains largely unknown (LeDoux & Pine, 2016). The principal aim of this study is to assess the utility of the fear-conditioning paradigm as a translational approach to understand pathological anxiety development. To this end, we explored variations in associative fear learning to identify potentially meaningful individual differences in fear responding. These different fear-learning patterns may in turn be related to underlying processes and to personality characteristics or clinical symptoms of anxiety (in line with the Research domain criteria (RDoC) approach of Briscione, Jovanovic, & Norrholm, 2014; Cuthbert, 2014).

Most experimental associative fear-learning studies focus on average fear responding and treat inter-individual differences as error variance (Lonsdorf & Merz, 2017). This central tendency approach precludes the identification of clinically relevant subpopulations with distinct response patterns (see for more discussion Gazendam et al., 2015; Lonsdorf & Merz, 2017). In fact, the sample mean may not adequately describe the response patterns of any individual and may not necessarily translate into useful information for subgroups of people (or patients) ('one size fits none rather than one size fits all', p.705 Lonsdorf & Merz, 2017). Indeed, clinical and epidemiological studies show that responses to aversive or threatening events strongly differ between individuals (as summarized by Galatzer-Levy, Ankri, et al., 2013). A classic point is that only a minority (e.g., 7%) of individuals exposed to trauma (> 75%) develops a posttraumatic stress disorder (PTSD) (Breslau & Kessler, 2001). Longitudinal studies have revealed clinically relevant heterogeneity in the course of PTSD-like symptoms, uncovering distinct profiles, with some people showing rapid adaptation with only transient symptoms (resilience), others showing slow remission (recovery), and again others showing failure to remit (chronic stress) (e.g., Bonanno & Mancini, 2012; Galatzer-Levy, 2014). For the fear conditioning model to have translational value, it needs to reveal meaningful individual variation in fear-learning trajectories in the laboratory as well. Furthermore, if heterogeneity in fear learning is detected, additional support for the translational potency of the fear-conditioning model will be provided when those diverse fear-learning patterns replicate (i.e., resemble) courses of anxiety development in real life.

It has been argued that the fear-conditioning manipulation posits a so-called strong situation, that is, a situation in which "an unambiguous threat of an imminent and dangerous stimulus evokes the

adaptive fear response” among all individuals alike (e.g., similar reactions in healthy controls or anxiety patients) (p.1, Ickes, 1982; Lissek, Pine, & Grillon, 2006). In other words, when the fear conditioning manipulations are strong, little room is left for the detection of individual differences. This would seriously limit the potential utility of the fear-conditioning model as a translational approach for studying abnormal fear. Most earlier studies have tested strong situations (Lissek et al., 2006) by testing fear acquisition, where a single cue followed by shock generally elicits fear. Analogous to rodent work, the first decades of research have utilized only CS1+ conditioning and not discriminative (CS1+/CS2-) associative fear-learning paradigms. As this fear acquisition reflects a highly adaptive response to impending danger (e.g., Frijda, 1986), it is not directly informative for understanding maladaptive fear. Moreover, real-life situations are often ambiguous; it may not be evident whether a cue signals threat or safety, and individuals have to rely on fast, automatic interpretation for responding (e.g., Caspi & Moffitt, 1993). Consistent with this view, individuals at risk for or suffering from anxiety disorders do not differ from healthy controls in fear for threat stimuli (see updated review on anxiety disorders Davis et al., 2015; and at-risk individuals e.g., Gazendam et al., 2015; Gazendam, Kamphuis, & Kindt, 2013; Haaker et al., 2015; Haddad, Pritchett, Lissek, & Lau, 2012) or negative interpretation of the threat stimuli (e.g., Mathews & Mackintosh, 1998), but show heightened fear responses to ambiguous cues (Lonsdorf & Merz, 2017; Tanovic et al, 2018). Note that the elevated fear to ambiguous (but safe) stimuli can also be regarded as fear generalization, which lies at the core of anxiety disorders (American Psychiatric Association, 2000). In the current experiment we therefore created so-called weak situations, by including test phases that are ambiguous, complex, or uncertain (Lissek et al., 2006). In addition to the CS1+, a CS2- is presented that will signal the absence of the UCS and becomes the control stimulus. We also include an extinction phase where the previously threatening stimulus is no longer followed by the aversive event (UCS), which typically results in the reduction of fear (extinction). Observed impairment in extinction learning allows for the study of persistence of fear (Scheveneels, Boddez, Vervliet, & Hermans, 2016), which is a hallmark of pathological anxiety. In addition, we included a fear generalization test assessing fear reactivity to two ambiguous stimuli (Glenn et al., 2012). In a similar vein, reinstatement was tested in which aversive stimuli (UCSs) were suddenly presented without a CS, a procedure seen

as analogue to triggering relapse of fear (Bouton, 2002), which was followed by a re-extinction phase. In sum, these ambiguous cues subsequent to acquisition may elicit more variability in fear response patterns between individuals.

We explored how heterogeneity in fear learning is manifested on different response dimensions of conditioned responding. Given that fear and anxiety, like any other emotion, are considered to be reflected in three loosely coupled response systems (i.e., behavior, physiological activity, and subjective experience; Mauss, Levenson, McCarter, Wilhelm, & Gross, 2005), we have used a multi-method approach across response systems. As different response measures tap into (partly) different underlying mechanisms (Lonsdorf et al., 2017), response measures may differ in the extent to which they reveal individual variation in fear-learning trajectories (Gärendt et al., 2015; Lonsdorf & Merz, 2017). To improve the translation of basic fear processes to pathological anxiety, it has been suggested that two types of threat responses are key to include: 1) behavioural and physiological reactions (defensive responses), and 2) conscious feeling states reflected in self-reports of fear and anxiety (LeDoux & Pine, 2016). Behavioural and physiological responses of fear are objective and can provide important insights in the neurobiology of fear (Bowers & Ressler, 2015). Studying self-reported distress is particularly relevant as these subjective experiences are the problems that lead people to seek help and are used daily in clinical settings (e.g., ‘subjective units of distress’ scale (SUD); Kaplan, Smith, Coons, 1995). To assess subjective and physiological conditioned response systems, we measured a) fear potentiation of the startle reflex, reflecting the defensive state physiology of an organism evoked by threat (negative valence and arousal) (e.g., Grillon & Baas, 2003), b) the skin conductance response, reflecting activation of the sympathetic arousal system (Venables & Christie, 1980) and c) distress ratings, which measure the affective response on a subjective level (e.g., Boddez et al., 2013), the apprehension characteristic of anxious individuals.

Finally, we assessed whether subgroups with distinct fear-learning trajectories differed in specific personality traits known to be associated with psychopathology in general, and with anxiety disorders in particular. If emergent fear-learning patterns are marked by different personality standings, this information may provide additional support that these fear-learning patterns can be considered ‘fear-conditioning related intermediate phenotypes’ (as proposed by Briscione et al., 2014). A common

approach for uncovering the relationship between fear learning and personality has been to compare the average fear response in a control group to a group ‘at risk’ for anxiety (i.e., high on a risk factor) (e.g., review by Mineka & Oehlberg, 2008). So far, the results of these studies are inconclusive (see review of (null) findings in Lonsdorf & Merz, 2017) and the mixed findings can in part be explained by the above-mentioned idea that (group) averages may reveal null findings and obscure meaningful variation (e.g., Kristjansson, Kircher, & Webb, 2007). An alternative explanation for the inconclusive findings is that most studies focused on one risk trait only, while fear development is likely affected by a combination of risk and resilience traits (e.g., Krueger, Caspi, & Moffitt, 2000; Tugade & Fredrickson, 2004). Further, given the importance of resilience factors for protecting against psychopathology (e.g., Fredrickson, Tugade, Waugh, & Larkin, 2002) - which are rarely included in experimental (fear) research – we included a dimension of Positive Emotionality (PEM), as low Positive Emotionality is associated with anxiety related disorders (Krueger, Caspi, & Moffitt, 2000; Miller et al., 2003, 2004) and theoretical work suggests that high levels of Positive Emotionality may exert protective effects (Clark, 2005; Krueger et al., 2000; Tellegen & Waller, 2008). More specifically, we selected a primary risk trait Stress Reaction (SR), a behavioural risk trait Harm Avoidance (HA), and a resilience trait Well-being (WB) (Krueger et al., 2000) from the personality model operationalized by the Multidimensional Personality Questionnaire (MPQ; Tellegen & Waller, 2008) (see Table 1 in Supplementary Material). The MPQ model measures normal personality variation, and has shown utility in generating general, at risk, and clinical profiles of personality (e.g., Eigenhuis, Kamphuis, & Noordhof, 2017; Krueger et al., 2000). Stress Reaction is strongly related to anxiety disorders (Krueger et al., 2000), and individuals high on Stress Reaction tend to expect, perceive, and (re-) experience catastrophes. In addition, as a meaningful distinction was shown between trait anxiety and trait fear, which has both clinical and theoretical implications (for a meta-analysis see Sylvers, Lilienfeld, & LaPrairie, 2011), we included the Harm Avoidance scale that measures fearfulness, the tendency to fear physical threat and avoid it.

The aim of this study was to examine individual variation in associative fear learning and to assess co-occurring personality standings in a representative young adult Dutch sample (e.g., in terms of gender, low-high social economic status, education). For uncovering distinct fear trajectories, we

performed Latent Growth Mixture Modeling (LGMM; Jung & Wickrama, 2008) using trial-by-trial conditioning data and including all phases simultaneously. LGMM allows identifying individual differences in fear learning by modeling latent subpopulations (classes) characterized by their fear response trajectories. We investigated three main research questions. First, we tested whether variation in fear learning (heterogeneity) could be detected. If models with multiple fear trajectories yield better fit to the data than a single trajectory model, this would suggest cohesive individual differences, and as such endorse the potential suitability of the associative fear-learning model as a translational model of pathological fear development.

Second, we examined whether common fear-learning ‘phenotypes’ of adaptive responding, maladaptive fear responding, and limited or non-responding could be observed, consistent with the heterogeneous course of risk and resilience for fear pathology in naturalistic studies (e.g., Bonanno & Mancini, 2012). Such studies have shown that in the aftermath of a traumatic event, individuals may show resilience, slow or delayed recovery, or develop a chronic disorder. To illustrate (see Method section and Box 1 for details), the maladaptive responding would be evidenced by one or more of the following conditioning processes: a persistence or generalization of fear responding to safety stimuli (i.e., the stimulus that has never been followed by an aversive event (CS2-), or the context), failure to extinguish fear responses to stimuli that originally predicted threat (CS1) but are no longer dangerous (i.e., CS1- from extinction onward), or a return of fear to stimuli that have never predicted threat but are similar to the original CS (Generalization stimuli). Conversely, adaptive patterns are defined by flexible learning, strong safety learning and extinction (largely in line with the conceptualizations of e.g., Bouton, 2007; Briscione et al., 2014; Galatzer-levy, Bonanno et al., 2013; Gazendam et al., 2013, 2015; Haaker et al., 2015; Haddad et al., 2012; Jovanovic et al., ; 2012; Lenaert et al., 2014; Lissek et al., 2005; Lonsdorf & Merz, 2017; Mineka & Oehlberg, 2008; Plendl & Wotjak, 2010). We also identified limited- or no responders; i.e., individuals who have shown no or limited variations across all learning phases. As limited responding cannot by itself be interpreted as either adaptive or maladaptive, we treated such data as a separate category. Limited responders have been reported in clinical studies (e.g., Bonanno, 2004), and a non-responders subgroup is typically observed in fear-conditioning work in both humans and animals, albeit often removed from the main analyses (see for

discussion Lonsdorf et al., 2017).

Third, we assessed whether subgroups with distinct fear-learning trajectories differed in specific personality risk (Stress Reaction, Harm Avoidance) and resilience (Wellbeing) traits known to be associated with psychopathology including anxiety disorders (Krueger et al., 2000). We hypothesized that more maladaptive fear-learning patterns would be characterized by *at risk* MPQ personality profiles, with higher levels of Stress Reaction and Harm Avoidance and a lower level of Wellbeing. Conversely, we predicted that more adaptive response patterns would be characterized by *resilient* MPQ personality profiles, with higher levels of Wellbeing and lower levels of Stress Reaction and Harm Avoidance. Lastly, we predicted that limited or non-responders, i.e., individuals showing no or limited variation in responding across conditioning phases, would be characterized by low levels of Stress Reaction and Harm Avoidance.

Materials and Methods

Participants

The present study was part of a larger individual differences project that took place at the University of Amsterdam. Participants were recruited from various backgrounds (8% had a non-Dutch native country), had Dutch nationality, and were representative of the Dutch population of young adults in terms of gender, socio-economic status, and educational level (see Centraal Bureau voor de Statistiek, 2011). The initial sample of the fear learning experiment consisted of 936 individuals. For each of the fear indices, several participants were excluded because of missing or invalid data (for details see Data reduction section). In addition, across fear indices, six participants were excluded because of excessive inconsistent responding as indexed by the MPQ response inconsistency scales (Eigenhuis, Kamphuis, & Noordhof, 2013). The final sample for our main analyses on the distress data consisted of 924 subjects (481 females and 443 males, mean age $24.61 \pm SD: 1.81 \pm$ years, range 21-28 years). The sample for the EMG analyses consisted of 893 subjects (465 females and 428 males), and the sample for the SCR analyses consisted of 670 individuals (313 females and 357 males) (for further details on the sample characteristics see Result section and online Supplementary Material). All subjects gave written informed consent to participate in the study, and the study had ethical approval of the ethics

committee of the University of Amsterdam. Participants received financial compensation for their participation.

Personality Assessment

The MPQ (Tellegen & Waller, 2008) assesses normal personality variation and provides coverage of a range of traits encompassing the domains of temperament, interpersonal and imaginative style, and behavioural regulation. The MPQ consists of binary, mostly True or False, items that cohere into 11 lower order scales, which in turn coalesce into three higher order factors that have clear temperamental and proposed psychobiological referents (Depue & Lenzenweger, 2011). The three factors higher order structure consists of Negative Emotionality (NEM), Positive Emotionality (PEM), and Constraint (CON). We employed the Dutch Brief Form of the MPQ (135 items) (MPQ-BF-NL; Eigenhuis et al., 2013). From the higher order factors, we selected the scales that had clear conceptual links to risk- and protective factors in the context of the fear-conditioning paradigm, namely Stress Reaction (SR; existential anxiety), Harm Avoidance (HA; fear), and Wellbeing (WB) (see Table 1 for descriptions of low and high scorers, Cronbach's alphas, and summary statistics in our sample). The descriptive characteristics are based on the sample with complete Distress data.

Predictors. Raw scale scores were transformed to normalized T-scores ($M=50$, $SD=10$), benchmarked on a representative Dutch sample (see Eigenhuis et al., 2013). Two-sided Z-tests revealed that, compared to the norm, in our sample the mean HA score was lower ($z = 16.38$, $p < .001$), the mean SR score was higher ($z = 4.11$, $p < .001$), and the mean WB score was lower ($z = -4.32$, $p < .001$) (see Table S1). Note that the differences in MPQ scores between our young adult sample and the general norms can be explained by the existing evidence that the manifestation of a trait depends on age and stabilizes over time (Eigenhuis et al., 2017; Roberts, Caspi, & Moffitt, 2011). That is, certain behaviour that is included in the questions of the HA scale fits a young adult sample: Constraint (the higher order factor of HA) increases with age (McGue, Bacon, & Lykken, 1993; Roberts et al., 2001) and SR is generally higher in young adults since neuroticism decreases with age (Roberts et al., 2001).

Stimuli

Conditioned stimuli (CS). The stimuli (CS1, CS2, and GS new) comprised of pictures of male faces

with a neutral expression (CS #090_07 and #090_15, and GS new: #090_71; Radboud face stimuli; Langner et al., 2010). In addition, we created a second Generalization test stimulus (GS morph) by morphing the CS1 (50%) and CS2 (50%) faces (software: <http://www.norrkross.com/software/morphx/morphx.php>) (similar morphing was done by Glenn et al., 2012). This morph stimulus thus consisted of a combination of the original safe and danger stimulus, forming an ambiguous cue. Individual differences may be expressed in how one individual resolves this ambiguity (e.g., whether the responses to the GSs are more similar to the danger or control stimulus).

Unconditioned stimulus (UCS). The UCS constituted of one 2-ms electric stimulus produced by a Digitimer DS7A constant current stimulator (Hertfordshire, UK). The UCS was administered to the non-dominant hand wrist via a pair of standard Ag/AgCl electrodes attached with electrolyte gel. UCS intensity level was determined by gradually increasing the intensity to a level that was ‘highly annoying but not painful’ (mean UCS intensity: $20.79 \pm \text{SD: } 15.27$ mA).

Measurements

Startle probe. The acoustic startle probe consisted of a 40-ms duration, 104 dB burst of white noise with a near instantaneous rise time, presented binaurally by headphones.

Physiological recording¹

Startle fear response. Potentiation of the acoustic startle reflex to a loud noise was measured by electromyography (EMG) of the right orbicularis oculi muscle.

Skin conductance response. Electrodermal activity was measured on the non-dominant hand (to prevent movement artifacts of the online ratings) using an input device with a peak-peak sine shaped excitation voltage (± 0.5 V) of 50 Hz.

Subjective ratings

Self-reported distress. Subjective distress was rated online during CS presentations by the question ‘How distressed or anxious do you feel at the moment?’ printed above a continuous visual analogue scale (VAS) anchored ‘Not at all distressed’ to ‘Somewhat distressed’ to ‘Very distressed’ (registered 0-200). Participants were instructed to provide online ratings by clicking on the point of the distress

¹ See supplementary material for full description of the physiological recording.

scale that corresponded to their distress or anxiety² within 4 s following CS presentation.

Retrospective recognition and risk ratings (Table S1 in Supplementary Material). For the *recognition ratings*, the CS1, CS2, GS morph, and GS new faces were presented and to minimize the odds of random ratings the stimuli were intermixed with four filler trials (F1-F4 consisted of similar neutral male faces; Langner et al., 2010). Recognition was indexed by ratings to the question ‘Have you seen this face?’, printed above a VAS anchored ‘Certainly not’ to ‘Uncertain’ to ‘Certainly’ (registered -100 to 100). Subsequently, *risk of occurrence of an electric stimulus* was rated for those stimuli that participants previously recognized (i.e., rated > 0) by the question ‘How likely did you consider the chance that this face was followed by an electrical stimulus?’ printed above a VAS anchored ‘Expected certainly no electric stimulus at that moment’ to ‘Uncertain’ to ‘Expected certainly an electric stimulus at that moment’ (registered from -100 to 100).

Experimental Design and Procedure

Fear conditioning task

Participants performed a discriminative fear conditioning procedure (see Figure 1). Due to the very large sample size, testing was restricted to a single session. During each session, first electrodes were attached, and thereafter UCS intensity was individually calibrated (see Stimuli). Next, participants received the instruction that one of two faces would sometimes be followed by an electric stimulus while the other face would never be followed by an electric stimulus. In the *Habituation* phase eight acoustic startle probes were delivered to stabilize baseline startle reactivity (Bradley, Lang, & Cuthbert, 1993) (inter-trial intervals (ITIs)³ varied between 9-13 s). In the *Fear Acquisition* phase, the threat stimulus (CS1) was reinforced in all but the first trial (84% reinforcement schedule). A relatively strong acquisition manipulation was chosen to enhance acquisition success, as initial discriminative learning is a necessary condition to be able to test our research questions in the subsequent phases. CS1, CS2, and NA trials were presented semi-randomly (i.e., in 6 sets, random presentation of each trial type). CS1 and CS2 were presented singly for 8 s. The startle probe was delivered 7 s after stimulus onset and for CS1 trials the UCS was delivered at 7.5 s. The ITIs varied

² Note that if a participant did not provide a rating (by a mouse click) within 5 s, the value corresponding to the position of the cursor was registered (i.e., the maximum (lowest or highest) value during the final 2 s of CS presentation).

³ To enhance their focus, participants were asked to attend to a fixation cross that was presented during each ITI.

between 17-21 s, and startle probes (Noise Alone trials, NA) were delivered (6 times) in these ITIs. After 11 s (during presentation of a white screen), in the subsequent *Extinction* phase, the unreinforced CS1⁻ (no UCS), CS2, and NA trials were presented semi-randomly (in 12 sets of each trial type). After another 15 s (during presentation of a white screen), during the *Generalization test*, GS new, and GS morph were each presented twice with two NA trials (note that half of the participants received as the first test trial the GS new and the other half the GS morph). After 15 s, one unreinforced CS1⁻ (no UCS), CS2, and NA trial were presented (Post-generalization test). Thereafter, following an ITI of 17 s, three unsigned UCSs were delivered (during presentation of a white screen) (after 15 s, 55 s, 85 s; Hermans et al., 2005) to induce return of fear, referred to as *Reinstatement test*, which continued after one ITI of 17 s into a *Relearning of extinction* (re-extinction) phase in which participants were again exposed to 4 sets of the CS1 (without the UCS), CS2, and NA trials (see Figure 1). Then, participants were instructed that this task was finished and that they would receive some additional questions. First a contingency question was presented, and thereafter they were asked to provide recognition and risk ratings of the CS1, CS2, GS new, and GS morph.

Data Reduction and Response Definition

Psychophysiological data. All physiological data were processed with VSRRP 98 v 8.0 (custom-build application, developed by Technical Support Group, UvA Psychology). Non-response trials were excluded.

Exclusion. Participants were excluded when more than 33 % of their data was missing or technical problems yielded incomplete data (e.g., apparatus, conductance of electrodes) (Distress n=6; EMG n=37; SCR n=29).

Distress. As our main interest was more on the individual differences/variation in the *course* of learning than on differences in level of responding, distress data were centered. However, as individual variation in distress is also reflected in differences in the level of distress (e.g., reporting being strongly distressed (e.g., distress rating 150) or not distressed at all (e.g., distress rating 20), we additionally included an individual's first raw distress rating (intercept).

Startle fear response (EMG). (n= 37). For the startle response data, an analog notch filter was set at 50 Hz to remove interference of the mains noise. The raw EMG signal was amplified and band-pass

filtered (28–500 Hz butterworth 4th order) (Blumenthal et al., 2005; Van Boxtel et al., 1998). Startle magnitude was defined as the amplitude (measurement unit: μV) of the first peak within a 20–200 ms interval following the startle probe onset. Trials with excessive baseline activity or recording artifacts were discarded by the Vsrp program. Outliers (> 3 SDs) were replaced by an individual's mean ± 3 SD (see Supplementary Material). To reduce inter-individual variation in baseline EMG activity (and to ensure the results (class membership) are not confounded by general responsivity of subjects), the raw EMG data were converted to proportional change scores $((\text{score} - \text{individual baseline}) / \text{individual baseline})$ (e.g., Tabachnick & Fidell, 2007; Walker & Davis, 2002). Baseline was determined as the average startle reactivity of an individual's NA trials of the entire experiment (e.g. Jovanovic et al., 2010).

Electrodermal activity (SCR). The skin conductance responses were calculated by subtracting a baseline of the mean 1 s before CS presentation from the maximum of the following 7 s during CS presentation (e.g., Milad, Orr, Pitman, & Rauch, 2003). Participants were excluded when more than 33 % of their data were missing, or when technical problems yielded incomplete data ($n = 29$). Further, SCR non-responders were defined as participants who failed to show acquisition of conditioned responding (i.e., no more than two CS1 acquisition trials exceeded $0.05\mu\text{S}$ (raw scores); e.g., Pace-Schott et al., 2009). Participants meeting these commonly used criteria for SCR non-responder were excluded from analyses ($n = 232$). Even though a considerable proportion of SCR non-responders is common, this large proportion suggests that part of the non-response could also be due to technical recording issues with a heterogeneous sample. Further, as the present study is focused on individual differences in learning and not on baseline differences in the magnitude of their SCR scores, the SCR data were mean-corrected (Lovibond, 1988; see also Lykken, Rose, Luther, & Maley, 1966).

Statistical Analyses

Latent Class Growth Analysis. We employed Latent Class Growth Modeling (LCGM; e.g., Muthén & Asparouhov, 2007) using the 'flexmix' package (Gruen, Leisch, Sarkar, Mortier, & Picard, 2013) in R (Team, 2016). LCGM is a modeling technique that is designed to detect heterogeneity in a population and to find groups of individuals who are similar in their growth

trajectories (Muthén, 2004). Growth trajectories are defined by the growth parameters (i.e., intercept and slope) (Nylund, Asparouhov, & Muthén, 2007). We ran separate LCGM analyses for each dependent variable (i.e., distress ratings, EMG, and SCR). We included all phases (with their responses to CS1, CS2, GS morph, or GS new) and estimated different parameters for different phases (piecewise model). By including all phases within the same analyses, rather than repeating all analyses for each phase separately, we ensured that the same participants were included in the same classes throughout the complete fear learning trajectory. Our modeling strategy was as follows. We first ran an LCGM with one class. Next, we progressively added 1 additional class to the model. We stopped when a model was detected with a Bayesian Information Criterion (BIC) value that was lower than the previous more parsimonious model, and also had a value that was lower or the same than the next more elaborate model⁴ (Schwartz, 1978). The BIC is widely regarded as a good indicator for class selection (Jung & Wickrama, 2008; Nylund et al., 2007). If the LCGM showed that the best fitting models were those models with more than one trajectory (class), this indicates the presence of different subpopulations within the sample and evidence for individual differences (heterogeneous growth trajectories).

Learning Assessment. Separately from the main LCGM analyses, we performed additional analyses to examine fear learning for the whole sample, as this is usually done in fear conditioning studies. For that, we ran for each measure CS-Type x Trial repeated measures Analyses of Variances (ANOVAs), for each conditioning phase, with CS-Type and Trial serving as within-subjects factors. The levels of both factors were determined per phase. For the CS factor the levels were CS1 and CS2 for the Acquisition, Extinction, Reinstatement, and the Re-extinction phases. For the Trial factor, for Acquisition, Extinction, and Re-extinction the levels were the same as the number of trials for each phase. As an additional extinction index the ‘completeness of (re)-extinction’ was assessed by testing whether responses to CS1 were still larger than to CS2 at the final (re)-extinction trials. For testing Reinstatement (comparing PG trial 1 to Re-extinction trial 1), generalization to the Morph (comparing Extinction CS2 trial 12 to GS Morph trial 1) and the New stimulus (comparing Extinction CS2 trial 12 to GS New trial 1), as well as the generalization course, we run separate paired sample t-tests for each

⁴ All models were run using different starting values and the resulting model with the lower BIC was selected.

measure (see also Supplement p.3). All analyses results can be found in the Supplementary Material. Here, we report their effect sizes. Specifically we consider a partial η^2 effect size above 0.0099 as a small effect, above 0.0588 as a medium effect, and above 0.1379 as a large effect (Richardson, 2011). For Cohen's d we consider values above 0.2 as small effects, values above 0.5 as medium effects, and for values above 0.8 as large effects (Cohen, 1988).

Analyses of the main Research Questions. *Research Question 1: Individual variation in fear learning.* For the first research question, we examined whether heterogeneity was revealed, that is, whether subgroups with substantively distinct trajectories were identified for Distress, SCR, and EMG separately.

Research Question 2: Fear learning intermediate phenotype. Subsequently, we assessed whether the distinct trajectories revealed common patterns of fear responding analogous to the heterogeneous patterns of anxiety development observed in response to real-life threatening events. This would provide evidence for 'intermediate fear-learning phenotypes'. We examined whether patterns could be identified, that range from more 'adaptive responding', that may mimic resilience or recovery, to less adaptive or 'maladaptive responding', that may resemble delayed/chronic fear, and 'limited or non-responding' patterns. Adaptive responding is generally defined by response patterns that would indicate that behaviour is adjusted to changing circumstances, e.g., learning that a stimulus is dangerous, safe, or no longer dangerous (see Box 1 left column). Less adaptive, or maladaptive responding can generally be defined by the impaired ability to reduce conditioned responses when threat is not or no longer present (see Box 1 right column).

For determining the extent to which each trajectory can be considered adaptive or maladaptive, we based our classification on the strength of fear and safety learning across four conditioning phases. For this, we examined the size of the effects (η^2 or Cohen's d) of the relevant analyses per phase as reported in Box 1 (for statistical results see Supplement). The four performance indices were: 1) Acquisition discrimination (CS1+ > CS2-) and decrease in conditioned responding (CR) to the control stimulus (CS2-), 2) Extinction learning or complete extinction, 3) Immediate safety learning after generalization to the new stimulus, 4) Re-extinction learning or complete re-extinction (see also Box 1). On each of these four criteria identified classes were scored as adaptive (A) or

maladaptive (M) (e.g., AMAM). Classes scoring three or four A-scores were classified ‘Adaptive’, and with three or four M-scores a class was considered ‘Maladaptive’. Further, a class was labeled ‘Intermediate’ with two A-scores and two M-scores. In addition, to be considered ‘responder’, conditioned responding during three or more phases should deviate more than 15% from their own baseline responsivity: If this criterion was not met, the class was classified as ‘limited responder’. Baseline refers to the following criteria for the different measures: an individual’s mean of all NA trials for EMG (see also explained above), the individual mean SCR, and for distress baseline refers to 0 (center of scale, to which the cursor returns every trial).

Box 1. From Adaptive to Maladaptive Associative Fear Learning		
<i>Phase</i>	<i>Adaptive</i>	<i>Maladaptive</i>
Acquisition (trial 1-6)	<ul style="list-style-type: none"> discrimination between responses to the threat (CS1+) and control (CS2-) stimulus increase in differential responding (CS1+ > CS2-) decrease in responding to the control stimulus (CS2-) 	<ul style="list-style-type: none"> no increase in differential responding (CS1+ \leq CS2-) increase in responding to the control stimulus (CS2-)
Extinction (trial 1-12)	<ul style="list-style-type: none"> decrease in differential (CS1- vs. CS2-) responses via a decrement in responses to the CS1- complete extinction at the end (no CS1- vs. CS2- difference at the last two extinction trials) 	<ul style="list-style-type: none"> persistence of elevated responding to the CS1- an increase in CS1- vs. CS2- difference no general reduction of responding to both CS1- and CS2-
Immediate safety learning (after fear generalization to a new stimulus)	<ul style="list-style-type: none"> a decrease in responding from the first to the second generalization test trial (GS trials 1-2) if no initial generalization increment had taken place: no change in responding from GS trial 1-2 	<ul style="list-style-type: none"> an increase or persistence of elevated responding from GS trial 1 to 2

<p>Re-extinction (trial 1-4)</p>	<ul style="list-style-type: none"> • a decrease in differential (CS1- vs. CS2-) responding • complete re-extinction at the end (no CS1- vs. CS2- difference at the last re-extinction trial) 	<ul style="list-style-type: none"> • no change or an increase in differential responding (CS1- vs. CS2-) • incomplete re-extinction (CS1- vs. CS2- difference at the last re-extinction trial) • no general decrease in responding to CS1- and CS2-
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Research Question 3: Individual variation in fear learning and personality profiles.

Afterwards, we tested if participants in the distinct classes differed in their level of the MPQ personality traits Stress Reaction, Harm Avoidance, and/or Wellbeing by running separate one-way ANOVAs. The levels of SR, HA, or WB were interpreted as low, medium or high in comparison to the classes of the present study. We examined whether classes with more adaptive trajectories were characterized by more resilient MPQ personality profiles (i.e., lower SR/HA and/or higher WB), and whether those classes demonstrating less adaptive response patterns were characterized by more at-risk MPQ personality profiles (i.e., higher SR/HA and/or lower WB).

Results

Descriptive statistics

UCS intensity, Contraceptives, and SES: Before moving on with our main analyses, we checked several factors for their potential effects on the fear conditioning manipulation, as the acquisition phase is the most standard tested manipulation (see for details Supplement). The electrical stimulus (UCS) intensity did not correlate with the acquisition index (i.e., CS1+/CS2- difference score of the final 2 acquisition trials) for any response measure (distress, EMG, SCR) (all p s > .93). Next, the use of contraceptives within females (n=290 contraceptives, n=179 no contraceptives) revealed no acquisition differences ($p = 0.45$; e.g., for sex differences see Cahill, 2006). Based on visual inspection, individuals across social-economic classes (SES) showed similar fear acquisition trajectories.

Evaluation of conditioned stimuli. As a general manipulation check, several questions evaluated

retrospectively the degree to which the participant recognized the stimuli and assessed the risk for a shock associated to a stimulus. In sum, participants recognized all stimuli (mean recognition ratings CS1 or CS2 > 88 and GS new or morph > 74 on a -100 to 100 scale), and the risk was adequately rated as highest for the threat stimulus and lowest for the control stimulus (mean risk rating CS1 > CS2, $p < .0001$). Further, relatively more risk uncertainty was rated for the GS morph than for the GS new ($p < .0001$; see for details Table 2 in Supplementary Material). Note that these risk ratings were not used as an index of contingency awareness as they were retrospectively assessed, and therefore neither included in individual differences analyses.

General fear learning patterns across measures (see Fig. 1 and Tables 3-5 in Supplementary Material)

First, we examined whether the fear learning manipulations were generally successful. Below we describe the mean patterns of conditioned responses, separate for each measure, for each phase. The effect sizes of the analyses per test(phase) are included in the text, separate overall patterns of Distress, EMG, and SCR are depicted in Figure 1 and the statistics are described in the Supplement (Tables 3-5 in Supplementary Material).

Acquisition. Fear responses increased for the threat stimulus (CS1+) and decreased for the safety stimulus (CS2-) indicating discriminative conditioning, showing a large acquisition effect for Distress, and small to medium effects for EMG and SCR.

Extinction. Differential extinction learning occurred for Distress (medium effect) and for SCR (small effect). For EMG no differential extinction (no effect) was observed, only a general decrease in EMG to both CS1- and CS2- was detected (large effect). At the end of extinction, extinction was incomplete for both Distress and EMG (last two trials CS1- > CS2-; Distress: medium effect, EMG: small effect), while for SCR extinction was complete (no effect).

Generalization. Upon the ambiguous tests, fear generalization was mainly indicated by a strong increase in fear from the end of extinction to the new stimulus (GS new), with effects sizes varying from very large (Distress) to medium (EMG and SCR). Upon the morphed stimulus (GS morph) the increment was small (for Distress and EMG) or absent (SCR).

Immediate safety learning. Upon the second GS trial, immediate fear reduction varied in strength. The greatly increased response to the new GS decreased with effect sizes varying from no overall effect (Distress) to small (SCR) and medium effects (EMG). Following the limited fear generalization to the GS morph, Distress, and startle EMG responses did not significantly decrease, while for SCR immediate safety learning was shown (small effect).

Reinstatement. Although presentation of the reminder shocks (UCSs) did not result in differential reinstatement (no effect) for Distress, it triggered a non-differential reinstatement (large effect). For EMG, modest differential reinstatement (small effect) and a moderate non-differential reinstatement occurred (medium effect). For SCR, overall, reinstatement was absent (no effects).

Re-extinction. As for Distress and startle EMG, reinstatement had resulted in increased fear to both CS1- and CS2-, differential re-extinction was absent (no effect) but responding to both CSs reduced (Distress: large effect; EMG: medium effect). At the end, re-extinction was incomplete for Distress (medium effect) and complete for EMG (no effect). For SCR, as no overall reinstatement was observed at first, no re-extinction could be revealed (no effects; and re-extinction was complete).

I. Individual variation in fear learning (Figures 2-4 and Table 2; Tables 6-12 and 18-26 in Supplementary Material)

We found that the LCGM analyses identified different models with substantively distinct growth curve patterns for Distress, EMG, and SCR (see Table 2). This indicates that, while in most studies only the general patterns (similar to our mean plots in Fig.1) are reported, the present LCGM analyses revealed heterogeneity. Specifically, 7 distinct classes of Distress responding (N=924), 5 distinct classes of EMG responding (N=893), and 4 distinct classes of SCR responding (N=670) were identified (see Figures 2, 3, 4, and Table 27 in Supplementary Material). This provides evidence for individual differences in fear learning on all emotional response domains. In addition, in nearly all phases, classes differed in their performance. Below we provide several examples of distinct trajectories, that may reflect meaningful differences in associative learning.

Distress. For the subjective Distress response (Fig. 2 and Tables 6-12 in Supplementary Material), classes differed strongly in their strength of discriminative acquisition, from medium effects (e.g., class G) to extremely large effects (class D). Similarly, classes demonstrated differences in their strength of generalization, with some showing small effects (e.g., class F) and others extremely large effects (class C).

EMG. Heterogeneity in associative fear learning is also illustrated by the startle fear response (EMG) (Fig. 3 and Tables 18-22 in Supplementary Material) whereby classes varied in their strength of acquisition from a medium effect (e.g., class C) to a small effect (class D). In addition, the strength of EMG generalization to the morph stimulus ranged from medium (class C) to small effects (class D, E), and reinstatement effects varied from no differential reinstatement (class E and D) to medium effects (e.g., class C).

SCR. Differences in fear and safety learning were slightly smaller but also evident for the SCR (Fig. 4 and Tables 23-26 in Supplementary Material), where the strength of acquisition varied from small effects (class C, D) to medium effects (class A, B). Additionally, the degree of immediate safety learning (after the generalization of SCR to the GS morph) varied from a small effect (class C) to no effect (class B).

Summary I. Individual variation in fear learning

Taken together, differences were observed between individuals across response measures during all associative fear learning phases (i.e., acquisition, extinction, generalization as well as immediate safety learning, reinstatement, and re-extinction). Note that these distinct trajectories deviate from the mean trajectories; the patterns (and effects of each phase) of the subgroups show only partial resemblance to the general fear learning patterns. Furthermore, the data showed more distinct classes for Distress compared to EMG and SCR.

II. Fear learning ‘intermediate phenotypes’

With respect to our second main research question, we found that the distinct associative fear learning trajectories show considerable similarity to the heterogeneous patterns of fear development observed in response to real-life threat. The distinct Distress, EMG and SCR trajectories ranged from adaptive to maladaptive responding and included limited-responding patterns (see Figures 2, 3, 4 and Table 27 in Supplementary Material). More specifically, patterns were observed of a) strong safety learning or (re)extinction, resembling real life patterns of ‘resilience or recovery’, b) deficient safety learning or (re)extinction, resembling ‘delayed or chronic anxiety’, or c) limited reactivity, resembling ‘non-response’. Note that for SCR and EMG, no classes were marked as entirely maladaptive. For detailed

results of each class' trajectories for each experimental phase see the Supplement (Tables 18-26 in Supplementary Material). Note that for EMG, the extinction phase was not included to classify the fear learning patterns because no significant extinction was observed in any class (see Fig. 1 panel 2; Table 4 and Figures 3, 18-22 in Supplementary Material)⁵. Below we describe the classes and their fear-learning trajectories in the following order: from most adaptive, to intermediate, to maladaptive, ending with a description of the limited responders (see for details Method section and Box 1).

Distress - Adaptive patterns

The fear-learning patterns of four classes were considered adaptive (see Fig. 2 panels A-D, Tables 6-9 in Supplementary Material). The first Class A (n = 166; 18%; Fig.2 panel A, Table 6 in Supplementary Material) was considered most adaptive because of their strong safety learning. Specifically, acquisition discrimination (very large effect) with safety learning to the CS2- was found and strong extinction occurred (medium effect). In addition, safety learning was observed upon the second presentation of the new generalization trial (GS new), (medium effect) and re-extinction took place (small effect). The second adaptive class B (n = 113; 12%; Fig.3 panel B, Table 7 in Supplementary Material) was characterized by relatively low distress levels (e.g., raw distress ranged from approximately 50 to 70). In addition, this pattern is considered adaptive because this class demonstrated acquisition discrimination (very large effect) including safety learning to the CS2-, extinction (medium effect), and immediate safety learning (medium effect) after the generalization of distress to the new GS (large effect). The specific strength of the third adaptive trajectory in Class C (n = 136; 15%; Fig.2 panel C, Table 8 in Supplementary Material) was their strong extinction performance. Following acquisition discrimination (very large effect) with strong safety learning to the CS2-, we observed substantial extinction (large effect) and immediate safety learning upon the second new generalization test trial (medium effect). Re-extinction was also demonstrated (large effect), but this remained incomplete (large effect). The final adaptive Class was D (n = 220; 24%; Fig.2 panel D, Table 9 in Supplementary Material) because flexible learning was shown. Specifically, strong acquisition discrimination (very large effect) was observed with safety learning upon the CS2-,

⁵ None of the classes showed 'successful' extinction or re-extinction according to the ANOVAs (no significant CS-Type x Trial effects, all $F_s < 1.8$; see Tables 15-19 in Supplementary Material).

followed by extinction (medium effect). In addition, immediate safety learning after generalization was demonstrated (small effect). However, for re-extinction only a general reduction to both CS1- and CS2- was shown (large effect).

Distress - Maladaptive patterns

Conversely, two patterns of persistence of high distress and distress increment (upon stimuli that are safe or no longer dangerous) indicating maladaptive responding were detected (see Fig.2 panels E-F).

The maladaptive pattern in Class E (n = 117; 13%; Fig.2 panel E, Table 10 in Supplementary

Material) was characterized by weak safety learning. Specifically, although acquisition discrimination was present (large effect), the effect size was smaller than previous classes (A-D) and safety (CS-

learning was absent (see Fig.2 panel E). Weak safety learning was further illustrated by neither

extinction (no effect), nor immediate safety learning following generalization of distress (no effect).

Although there was evidence for re-extinction learning (small effect), re-extinction was not complete

at the last trial (medium effect). Compared to all other distress classes, the most maladaptive Class F

(n = 110; 12%; Fig.3 panel F; Table 11 in Supplementary Material) was characterized by the weakest

safety learning combined with the highest persistent distress. In specific, although acquisition

discrimination appeared (large effect), distress to the control stimulus (CS-) even increased.

Subsequently, we observed weak extinction (small effect), a lack of immediate safety learning after

the generalization test (no effect), and re-extinction was absent (no effect). In sum, for this class the

initial highest distress levels persisted until the end.

Distress - Limited responders

Finally, we identified a class of participants that exhibited limited signs of subjective distress learning.

The pattern from acquisition to re-extinction of this relatively small class G (n =62; 7%;Fig.3 panel G;

Table 12 in Supplementary Material) can be summarized by 'persistent low distress' (range 0-20).

Although the statistical analyses suggest initial evidence for acquisition (medium effect), the range of

responses does not meet the criteria of 'responders' (see Method and Box 1). Further, the acquisition

was weakest compared to all other distress classes and this small differential responding immediately

diminished during extinction (small effect). Only for this subgroup, differential distress had

completely disappeared following generalization and reinstatement tests, at the end of re-extinction (no effect).

EMG - Adaptive patterns

For EMG, two trajectories of strong safety learning and extinction reflected more adaptive patterns (see Fig.3 panels A, B). Class A was classified as most adaptive (n=179; 20%; Fig. 3 panel A, Table 18 in Supplementary Material), demonstrating flexible learning and strong safety learning.

Specifically, acquisition discrimination (small effect, which was average for EMG) with a substantial decrease to the control stimulus CS2- were observed, and immediate safety learning (medium effect) was demonstrated after the EMG generalization to the new stimulus. Upon the reminder shocks, differential reinstatement was shown (small effect) followed by a general reduction (medium effect) that resulted in complete re-extinction (no effect). The EMG pattern of class B (n=271; 30%; Fig.3 panel B, Table 19 in Supplementary Material) was characterized by relatively low startle EMG levels (i.e., proportional change scores ranged from 0-0.6). Differential acquisition was observed (small effect), and EMG to CS2- decreased. During extinction, only a general reduction (large effect) was shown. After generalization, immediate safety learning occurred (small effect), and following nondifferential reinstatement (large effect), re-extinction was complete (no effect).

EMG - Intermediate patterns

The Class C (n=277; 31%; Fig.3 panel C, Table 20 in Supplementary Material) was considered intermediate because safety learning was partially present but extinction was weak. Specifically, acquisition discrimination was shown (small effect), with a decrease in startle EMG to CS-. Upon initial startle EMG generalization to the new stimulus (large effect) immediate safety learning was demonstrated (medium effect). Subsequently, a non-differential reinstatement to all stimuli (large effect) was shown. Although re-extinction resulted in a reduction of startle EMG to both CSs (large effect), at the last trial re-extinction was not yet complete (small effect).

The second intermediate startle EMG pattern in Class D (n=54; 6%; Fig.3 panel D, Table 21 in Supplementary Material) differed from the other classes in their remarkably strong and variable EMG reactivity (proportional change scores varied from 0-3), and was characterized by adequate acquisition

but deficient extinction and overgeneralization of fear. The high reactivity was first evidenced by the largest increases in startle EMG and impaired habituation⁶. Furthermore, the strongest discrimination between the threat (CS1+) and the control stimulus (CS2-) (medium effect) occurred, with safety learning to the CS2-. Similarly, this differential EMG responding persisted during extinction (small effect), which remained incomplete (medium effect). Following strong EMG generalization (large effect), some immediate safety learning took place (small effect). Reinstatement of EMG was observed specifically to the safe cues (CS2- and context) and despite the subsequent general EMG reduction (large effect), re-extinction remained incomplete (small effect).

EMG - Limited responders

Lastly, we identified a subgroup that exhibited limited signs of EMG learning across conditioning phases. Class E (n=112; 12.5%; Fig.3 panel E; Table 22 in Supplementary Material) was characterized by persistent low EMG levels that showed little variation across all phases (proportional change scores ranged from 0-0.3).

SCR - Adaptive patterns

Class A reflected the most adaptive SCR pattern (n= 182; 27%; Fig.4 panel A; Table 23 in Supplementary Material) by demonstrating strong SCR discriminative acquisition followed by strong safety learning. Specifically, strong SCR discrimination (medium effect) with a decrease in SCR to CS2- took place, and extinction was complete (no effect). Also, strong immediate safety learning (medium effect) followed the initial SCR generalization to the new stimulus (large effect), and after a modest differential reinstatement (small effect), re-extinction took place (small effect) which was not yet complete (small effect).

The second adaptive SCR pattern was revealed for the largest Class B (n=251; 37.5% Fig.4 panel B; Table 24 in Supplementary Material) by showing initial acquisition followed by rapid extinction and no return of fear. Specifically, SCR discrimination was successful (medium effect) with a decrease in SCR to the CS-, and was followed by immediate and nearly complete extinction (small effects). Initial generalization of SCR to the new stimulus (large effect) was followed by strong safety

⁶ Note that the observation that EMG continued to decrease across all trials indicated that the initial habituation procedure had not been sufficient for stabilizing the EMG reactivity of this class.

learning (medium effect). Subsequently, SCR remained persistently low, indicating an absence of reinstatement (no effect) and complete re-extinction (no effect).

SCR - Intermediate patterns

In contrast, an intermediate SCR trajectory was detected in the small Class C (n=61; 9%; Fig.4 panel C; Table 25 in Supplementary Material), characterized by highly variable SCR reactivity, weak extinction, but evidence for safety learning. Specifically, first, acquisition discrimination (medium effect) was observed, showing both strong threat (CS1+) acquisition and a decrease in SCR to the CS2-. Subsequent extinction performance was absent (no effect), and the SCR increase to the safe stimulus (CS2-) suggests some overgeneralization of fear. Following generalization to the new GS (large effect), immediate safety learning was demonstrated (medium effect). However, afterwards, a return of conditioned responding by differential SCR was shown (at the PG trial) that persisted, resulting in incomplete re-extinction (small effect).

SCR - Limited responders

Compared to all SCR classes, Class D (n= 176; 26%; Fig.4 panel D; Table 26 in Supplementary Material) persistently showed the least SCR reactivity (mean-corrected SCR varied from 0-0.25 μ S). Although some initial SCR acquisition discrimination (small effect) with a little decrease in SCR to CS2- was found, the immediate extinction (small effect) was complete (no effect). Except for a SCR response upon the new stimulus (medium effect) which immediately disappeared (medium effect), SCRs did not vary from the first extinction trial until the end (i.e., no reinstatement effect and complete re-extinction (no effect)).

Summary II. Fear learning intermediate phenotypes

Taken together, these findings showed that across all indices of fear, multiple distinct adaptive, intermediate, and maladaptive fear-learning trajectories emerged. In addition, several subgroups demonstrated limited responsivity. Most of the observed trajectories resembled common fear

development patterns seen in response to real-life threatening events.

III. Individual variation in fear learning and MPQ personality traits

Given our third research question, we tested whether the different classes of fear learning trajectories were characterized by differences in the selected personality traits, Stress Reaction, Harm Avoidance, and/or Wellbeing (see for details Table 13 in Supplementary Material). For EMG and SCR, the distinct classes did not significantly differ on the traits (for EMG all F s < 1.6; and for SCR all F s < 1). Notably, the seven distinct Distress classes were characterized by small differences in Harm Avoidance, $F(6,917) = 2.50, p = .03, \eta^2 = 0.02$. In addition, a trend was found for the between-class differences in Stress Reaction, $F(6, 917) = 1.80, p = .09, \eta^2 = .01$, and no differences were found for Wellbeing, $F(6,917) < 1$. As each distress trajectory has been described in detail in section II, we provide a brief summary in which we link the differences in fear and safety learning patterns to differences in Harm Avoidance (i.e., low, medium, or high level relative to the other classes).

Distress trajectories and their Harm Avoidance levels (Fig. 2 and Tables 6-13 in Supplementary Material)

As predicted, the four subgroups with the adaptive distress trajectories were characterized by low to medium levels of Harm Avoidance (Fig. 2 panels A-D, Tables 6-8 in Supplementary Material). Class A with the most adaptive learning trajectory was characterized by medium Harm Avoidance. These average harmavoidant individuals showed flexible learning and strong safety learning across all phases of acquisition, extinction, and generalization. The second adaptive Class B consisted of relatively low harmavoidant persons and showed a pattern of stable, low distress; they showed rapid extinction after discriminative acquisition, and immediate safety learning after small generalization of distress. The third adaptive Class C was characterized by medium Harm Avoidance, and a specific strength was their strong safety learning and (re)extinction. The final Class D demonstrating an intermediate adaptive trajectory was characterized by medium Harm Avoidance. Their distress learning pattern can be considered partially adaptive, as flexible (safety) learning was shown but (re-)extinction was

weaker compared to the other adaptive classes (A-C).

In contrast, the classes with maladaptive distress trajectories were characterized by relatively high levels of Harm Avoidance (Fig.2 panels E-F, Tables 10, 11 in Supplementary Material). Class E was characterized by medium-high Harm Avoidance and showed, compared to other classes, impaired discrimination between threat and safety. Specifically, distress upon the safe stimuli did not decrease (no safety learning) and no (re-)extinction was demonstrated. The second maladaptive Class F showed the most persistent high distress and was characterized by relatively high Harm Avoidance. Compared to other classes, the largest deficits in safety learning were observed, distress to the control stimulus continued to increase, and these highest distress levels persisted until the end of re-extinction.

Finally, Class G exhibiting limited distress was characterized by the relatively lowest levels of Harm Avoidance (Fig.2 panel G, Table 12 in Supplementary Material). From acquisition to re-extinction, the distress ratings of this low harmavoidant subgroup were lowest and barely changed (range 0-20).

Summary III. Individual variation in fear learning and personality profiles

Whereas no associations were observed between personality traits and the EMG and SCR subgroups, tentative evidence was found for an association between Harm Avoidance levels and the respective subgroups based on subjective distress (See Table 3). The results suggest that the associative distress learning patterns were adaptive in individuals relatively low to medium on Harm Avoidance and became more maladaptive with higher Harm Avoidance levels. This result was corroborated in post-hoc analyses showing a significant difference between the maladaptive group with the highest Harm avoidance score ($N = 110$), and the adaptive group with the lowest Harm avoidance score ($N = 113$) (see Table S28 in the Supplementary Material). In addition, a pattern of limited distress responding was revealed in the lowest harmavoidant subgroup.

Discussion

We investigated individual differences in associative fear learning in a representative Dutch young

adult sample ($N=936$). The main findings of our study provided mixed support for the heuristic value of the fear-conditioning paradigm as a translational model for understanding individual differences in fear learning and the development of abnormal anxiety. Our results present evidence for the existence of individual variation in associative fear learning, and show that these distinct fear-learning patterns in the laboratory resemble risk and resilient trajectories following a traumatic event outside the laboratory. However, few and weak associations were shown between the distinct trajectories of fear and safety learning and the selected risk- and resilience personality traits.

More specifically, we observed heterogeneity, as evidenced by variability in the course of fear learning on all measures of fear and anxiety. Our results demonstrate that models containing multiple learning trajectories provide a better fit to the data than models consisting of a single (average) trajectory. This heterogeneity in fear learning corroborates previous work in animals (e.g., Galatzer-Levy et al., 2014; Galatzer-Levy, Bonanno, Bush, & LeDoux, 2013) and is in line with our previous study in humans (Gazendam et al., 2015). Furthermore, our findings revealed that trajectories of the subpopulations largely deviate from the average pattern, indicating that a focus on (only) mean responding may hinder the identification of (clinically) relevant subpopulations.

Second, the majority of the distinct fear-learning trajectories resembled common courses of fear development. The observed adaptive, intermediate, maladaptive, or limited response patterns replicate resilient and risk responses observed in reaction to real-life threat reported in both experimental research (e.g. animal conditioning) and clinical studies (e.g., Bonanno, 2004; see Introduction). To illustrate, the current adaptive trajectories of strong safety and extinction learning and the maladaptive patterns of weak safety learning are in line with rodent studies that have revealed subpopulations showing either rapid extinction or failure to extinguish (summarized in Galatzer-Levy, 2014). The present trajectories also mimic longitudinal clinical studies on the course of PTSD symptoms (e.g., Bonanno, 2004; Bonanno & Mancini, 2012). These studies have revealed that after a traumatic event, some individuals demonstrate rapid adaptation with only transient symptoms (here: strong extinction following strong acquisition discrimination), others remit slowly (here: weak (re)extinction), and others fail to remit (here: no (re)extinction or safety learning). Lastly, we have also identified classes of participants that exhibited limited signs of learning across conditioning phases for

each response measure. Limited responders have been reported in clinical studies (e.g., Bonanno, 2004) and are observed in fear-conditioning work in both humans and animals (see for discussion Lonsdorf et al., 2017).

No relationships between the physiological fear-learning patterns and the personality profiles were observed, and few meaningful associations were found between personality and subjective distress responses. The seven distinct distress trajectories were associated with subtle differences in individuals' Harm Avoidance levels, trend differences in Stress Reaction levels, and no relationship with Wellbeing was observed. Although the differences in Harm Avoidance levels were small, results were in line with our hypotheses: more adaptive response patterns were associated with lower levels of Harm Avoidance, while the reverse patterns of maladaptive responding were related to relatively higher Harm Avoidance levels. Further, the subgroup that indicated least distress and showed no changes in distress consisted of individuals lowest on Harm Avoidance. As the differences in Harm Avoidance levels between the subgroups were small, data should be interpreted with caution. In the classes with higher Harm Avoidance levels this sensitivity to danger cues combined with their "better safe than sorry" strategy may explain the observed persistence of fear and impaired safety learning and extinction. These findings corroborate the results of a review revealing an association between trait fear and impaired extinction (Sylvester et al., 2011).

Whereas the results for subjective distress indicated many distinct classes that were also characterized by differences in the selected MPQ personality traits, our results for the physiological measures were quite limited. Compared to distress, for EMG and SCR fewer distinct learning patterns were identified (i.e., a smaller number of patterns and no strongly maladaptive class for SCR), more limited-responders were detected, and no relationships with MPQ personality traits were observed. The latter finding that personality traits relate to subjective and not to psychophysiological indices of fear corroborates previous work showing that a personality trait (i.e., anxiety sensitivity) was related to subjective fear-related complaints (i.e., SUDs, panic symptoms), but not to SCR or cardiac responses (e.g., Forsyth, Palav, & Duff, 1999). However, these findings are at odds with other studies where relationships between personality and physiology were detected (e.g., for EMG, but not SCR: Gazendam et al., 2015, 2013; for SCR: Pineles, Vogt, et al., 2009). To explain the current relatively

limited results on physiological measures, we need to take into account the potentially suboptimal measurement of EMG and SCR, that may be due to several characteristics of this large-scale study. To illustrate, given the large number of participants and long duration of the study, measurements were carried out by different experimenters, which inevitably causes noise in the data. Note that difficulties in obtaining an optimal measurement of startle responding (EMG) have been previously acknowledged (e.g., Blumenthal et al., 2005). We also note that although the present selection of MPQ scales is relevant in the context of fear and anxiety, there is yet limited existing evidence for the role of these traits in fear conditioning. Future work examining fear learning profiles should focus on other personality traits that have been reliably linked to differences in associative learning, such as intolerance of uncertainty or distress tolerance (Morris, 2019; Morris & van Reekum, 2019; San Martin, Jacobs & Vervliet, 2020). In addition, to specifically assess associations between traits and fear conditioning, alternative statistical approaches could be powerful (e.g., linear mixed models).

A closer look at the fear-conditioning data reveal that between-individual variation was observed on all response measures, across all phases, including the fear acquisition phase where individual variation was less expected since this is also viewed as a ‘strong situation’ (Lissek et al., 2006). Specifically, inter-individual differences in discriminative fear acquisition appeared for Distress, EMG, and SCR. These observations partly contradict limited (group) differences in threat acquisition that we found in our previous studies (Gazendam et al., 2015, 2013) and challenge the view that all individuals exhibit similar responses during (presumed ‘strong situations’ like) acquisition (Beckers, Krykoss, Boddez, Effting, & Kindt, 2013; Lissek et al., 2006). It may be hypothesized that most previous studies were not able to detect heterogeneity in fear acquisition because conditioned responding was studied in homogeneous samples and analyses were based on averages, whereas with the present methodology and a large heterogeneous sample more variation is uncovered⁷.

To translate basic research to clinical phenomena, it seems especially relevant to consider both physiological as well as subjective responses (e.g., LeDoux & Pine, 2016). Distress ratings showed

⁷ As the first CSs were not reinforced, CSs were quite similar, it is possible that present acquisition was less ‘strong’ compared to other acquisitions with 100% reinforcement or a single CS+ design.

sensitivity in terms of detecting individual differences in fear conditioning, and showed meaningful associations to trait risk factors for anxiety. This is not to say that the study of fear should be limited to subjective report, as other read-outs of fear such as autonomic or behavioural responses are informative as well (e.g., Fanselow & Pennington, 2018). For research into *maladaptive* fear however, it seems that collecting data on subjective feelings of distress is especially important given that a) distress ratings show strong resemblance to the SUD scale used in clinical practice (Kaplan et al., 1995), b) therapies are judged as successful largely on the basis of their capacity to change these subjective distress experiences (e.g., LeDoux & Pine, 2016), and c) subjective distress forms a core aspect of both personality risk factors and anxiety disorders.

Several implications can be derived for future experimental and translational research on anxiety. The results show the existence of multiple pathways to adaptive or maladaptive fear learning. It can be hypothesized that these different maladaptive trajectories may put an individual at risk for different subtypes of anxiety or stress symptoms. To illustrate, it may be speculated that the observed pattern of high fear to the threat and control stimulus that persisted until the end (Fig. 2, panel F) may reflect overactivation of the fear system, and lead to a chronic hyperarousal state. Likewise, a pattern of impaired discrimination between threat and safety (Fig. 2, panel E) may lead to overgeneralization of fear, while the limited-responsiveness pattern (Fig. 2, panel G) may for instance suggest a state of numbness or low arousal sensitivity. Another implication following inspection of the entire fear-learning trajectories is that an impairment in learning in a single phase does not necessarily imply deficient learning in other phases. For example, although a subgroup first showed deficient safety learning during acquisition, in subsequent phases (e.g., extinction, generalization) safety learning could be intact. Conversely, adaptive responding upon the initial threat does not guarantee strong safety learning in later phases; e.g., persons showing adequate safety acquisition and initial extinction can demonstrate maladaptive responding upon ambiguous cues or appear vulnerable to relapse (reinstatement). Future experiments could test whether and how learning deficits predict subsequent persistence of fear at later fear memory tests. A next step in the translation of basic fear processes to anxiety is to address the prospective validity of strengths or deficits in associative fear learning for (clinical) anxiety symptoms. Building on the tentative evidence that maladaptive responding during

fear conditioning predicted higher anxiety symptoms at six months follow-up (Lenaert et al., 2014), systematic investigations on this prospective validity are important. Another general implication of our findings is that the adaptive or maladaptive conditioned response trajectories provide evidence for the concept of ‘fear-conditioning-related intermediate phenotypes’ (Briscione et al., 2014; Cuthbert, 2014). Additional support for this idea of intermediate phenotypes is provided by the current and previous evidence that maladaptive fear-learning patterns were associated with higher levels of anxiety vulnerability traits (e.g., Gazendam et al., 2015, 2013; but results are mixed, see review by Lonsdorf & Merz, 2017). Given the proposition that personality serves as a diathesis for anxiety and stress disorders (e.g., Mineka & Oehlberg, 2008), conditioned response patterns may present candidate (psychological) processes mediating the link between more distal personality structures and anxiety disorder development. An example of a candidate process explaining how a trait may confer risk for anxiety are the presently observed deficiencies in safety learning in more harmavoidant (and stress reactive) subpopulations (largely in line with Gazendam et al., 2015, 2013).

Some other considerations and limitations of the present study should be mentioned. First, the robustness of our classification of the adaptive/maladaptive trajectories should be tested in future work. Second, we should be cautious in interpreting the findings from the limited-responders subgroup as these are likely composed of miscellaneous subgroups. For example, limited responses could reflect general low reactivity or, alternatively, point to an automatic or deliberately employed lack of ‘fearfulness’. This limited responding can be viewed as adaptive, as limited fear is acquired, but also as maladaptive as these (low anxious) individuals may be prone to repetitively putting themselves in dangerous or risky situations because of their initial weak conditioning. Further, limited responding could also be due to factors as suboptimal manipulations or (technical) recording of variation in physiological responses. Note though that the experiment was conducted using standard research protocols (see for EMG guidelines: Blumenthal et al., 2005; and for fear conditioning: Lonsdorf et al., 2017). Third, we acknowledge that the observed associations with selected personality traits were very limited. Possibly, the fear-conditioning experiment may not fully elicit the tendencies associated with a specific trait. For example, the fear conditioning task we used does not allow for any effective (harm) avoidance behaviours, and the amount of stress generated by the experimental manipulation

may not be sufficient to trigger strong individual differences in Stress Reaction. An alternative explanation is that personality effects may have cancel out across learning phases when these are analyzed over the entire course of fear learning, as was the case in our latent class analyses. With respect to the null effects for Wellbeing, it seems possible that this specific experimental task (fear conditioning) may not tap into the processes by which this protective factor contributes to resilience (e.g., arranging social support). Finally, whereas our sample was representative of the Dutch population in terms of gender, socio-economic background, and educational level, to further assess the generalizability of the data in future studies it can be useful to include other aspects of identity (e.g., gender identity, ethnicity). Relatedly, as we used only white, male faces as CSs we cannot exclude the possibility that there could be differences in conditioned responding based on the gender and ethnicity of the individuals.

To conclude, the present integration of associative fear learning along with individual differences supports and clarifies the translational value of the fear-conditioning paradigm. More specifically, this approach provides another avenue for studying ‘intermediate phenotypes’ underlying the dysregulated fear learning seen in anxiety-related disorders.

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Table 1. Description of Low and High Scorers and the reliabilities (alpha) for the selected MPQ Scales Stress Reaction, Harmavoidance and Wellbeing, and the Means and Standard Deviations (T-scores)

Scales	Description of a low scorer	Description of a high scorer	Reliability of the scale (N=924)	
			Cronbach's alpha	Mean (SD)
Stress Reaction	Can put fears and worries out of her (his) mind; quickly gets over upsetting experiences; is not troubled by emotional turmoil or guilt feelings.	Is tense and nervous; is sensitive, feels vulnerable; is prone to worry and feel anxious; is irritable and easily upset.	$\alpha = .846$	46 (9.37)
Harm Avoidance	Does or would enjoy dangerous and exciting experiences and activities.	Avoids excitement and threat; prefers safe activities even if they are tedious.	$\alpha = .752$	40.74 (10.83)
Wellbeing	Seldom really happy; Does not seem to experience excitement and fun in life	Optimist; Feels good about self; Sees bright future; Enjoys things (s)he does	$\alpha = .822$	51.86 (10.59)

Table 2. Model Solutions

Distress

Number of classes	AIC	BIC
1	525705.1	525722.7
2	513967.5	514011.4
3	504894.5	504964.7
4	500850.6	500947.2
5	498467.8	498590.7
6	496572.2	496721.4
7	495681.2	495856.8

EMG

Number of classes	AIC	BIC
1	151228.0	151246.2
2	132955.4	133000.9
3	128441.3	128514.2
4	126576.3	126676.5
5	125749.7	125877.3

SCR

Number of classes	AIC	BIC
1	83170.90	83187.74
2	49205.36	49247.45
3	41215.05	41282.39
4	37509.44	37602.04

Table 3. ANOVAs testing whether the fear learning subgroups (for Distress, EMG and SCR) differed in terms of the selected personality traits (SR, HA and WB).

	Stress Reaction (SR)	Heart Avoidance (HA)	Wellbeing (WB)
Distress	$F(6, 917) = 1.8, p = 0.0$, $\eta^2_G = 0.012$	$F(6, 917) = 2.503, p =$ $0.021, \eta^2_G = 0.016$	$F(6, 917) = 1.006, p =$ $0.420, \eta^2_G = 0.006$
Startle responses (EMG)	$F(4, 888) = 1.5, p =$ $0.180, \eta^2_G = 0.007$	$F(4, 888) = 0.473, p =$ $0.756, \eta^2_G = 0.002$	$F(4, 888) = 0.288, p =$ $0.886, \eta^2_G = 0.001$
Skin Conductance Responding (SCR)	$F(3, 666) = 0.425, p =$ $0.73, \eta^2_G = 0.002$	$F(3, 666) = 0.194, p =$ $0.900, \eta^2_G < 0.001$	$F(3, 666) = 0.227, p =$ $0.877, \eta^2_G = 0.001$

Legends

Figure 1. (Design) Schematic representation of the experimental design and stimuli used in the task. Stimuli were selected as neutral male faces from the Radboud face stimuli (Langner et al., 2010). 1-12= number of trials. CS1+=threat stimulus paired with an electrical stimulus (UCS) during acquisition; CS1- original threat stimulus not paired with an electrical stimulus; CS2-=control stimulus, never paired with an electrical stimulus; NA= noise alone trials (startle probe during the inter-trial-intervals; ITIs); GS=generalization stimulus. GS morph=stimulus created by morphing the CS1 and CS2; GS new= novel male neutral face stimulus; Flash symbol: electric stimulus (UCS). The CS1 and CS2 stimuli were counterbalanced; For half the participants, the blonde face was the CS1 and the brunette face was the CS2 and this was reversed for the other half. **(Plots) General fear learning patterns across phases per conditioned response measure.** Conditioned responses during the phases of acquisition (A1-6 trials), extinction (E1-12), generalization (G1-2), post-generalization (PG1), reinstatement and re-extinction (R1-4). First panel: Subjective distress ratings. Original scale was anchored from 0 to 200, distress ratings were centered (by subtracting the mean of the first CS1 and

CS2 acquisition trial from all values). *Note:* The first value (A1R) reflects the raw (uncentered) distress rating of the first trial; raw CS1 = open circle, raw CS2 = open square. Number of participants with valid data = 924. Second panel: Fear potentiated startle responses (EMG, in μV). EMG data were converted to proportional change scores (score – individual baseline) / individual baseline) (e.g., Tabachnick & Fidell, 2000; Walker & Davis, 2002). Number of participants with valid data = 893. Third panel: Skin conductance responses (SCR, in μS). SCR data were mean-corrected (e.g., Lykken et al., 1966). Number of participants with valid data = 670.

Figure 2. Trajectories of Subjective Distress Ratings (N = 924). Each plot represents the latent populations of distress responses identified using Latent Class Growth Modeling. On the x-axis each point represents a trial. The first value reflects the raw (uncentered) distress rating of the first trial (A1R); raw CS1 = open circle, raw CS2 = open square. Phases: A = Acquisition (1-6); E = Extinction (1-12); G = Generalization; PG = Post-generalization; R = Re-extinction (1-4). Note that Re-extinction follows Reinstatement of fear, which is tested following three unsignaled electrical stimuli (UCSs). On the y-axis, the subjective distress ratings are depicted (centered). Data are centered by subtracting the mean of the first CS1 and CS2 trial of acquisition from all values. CS1 = threat stimulus followed by an electrical stimulus (UCS) during acquisition; CS2 = control stimulus, never followed by an electrical stimulus; GS morph = stimulus created by morphing the CS1 and CS2; GS new = novel male neutral face stimulus.

Figure 3. Trajectories of Startle Fear Responding (EMG) (N = 893). Each plot represents the latent populations of EMG responses identified using Latent Class Growth Modeling. On the x-axis each point represents a trial. Phases: A = Acquisition (1-6); E = Extinction (1-12); G = Generalization (1-2); PG = Post-generalization; R = Re-extinction (1-4). Note that Re-extinction follows Reinstatement of fear, which is tested following three unsignaled electrical stimuli (UCSs). On the y-axis, the EMG data are shown, converted to proportional change scores ((score – individual baseline) / individual baseline). CS1 = threat stimulus followed by an electrical stimulus (UCS) during acquisition; CS2 = control stimulus, never followed by an electrical stimulus; GS morph = stimulus created by morphing the CS1 and CS2; GS new = novel male neutral face stimulus; NA = Noise Alone (startle probe during the inter-trial-intervals (ITIs), context).

Figure 4. Trajectories of Skin Conductance Responding (SCR) (N = 670). Each plot represents the latent populations of skin conductance responses identified using Latent Class Growth Modeling. On the x-axis each point represents a trial. Phases: A = Acquisition (1-6); E = Extinction (1-12); G = Generalization (1-2); PG = Post-generalization; R = Re-extinction (1-4). Note that Re-extinction follows Reinstatement of fear, tested following three unsignaled electrical stimuli (UCSs). On the y-axis, the SCR data were presented (in μS , mean-corrected). CS1 = threat stimulus followed by an electrical stimulus (UCS) during acquisition; CS2 = control stimulus, never followed by an electrical stimulus; GS morph = stimulus created by morphing the CS1 and CS2; GS new = novel male neutral face stimulus.

Highlights

- We detected heterogeneity in fear learning via latent growth curve modeling
- Subjective and physiological responding varied in both strong and weak test phases
- The distinct fear learning trajectories resemble risk and resilient sub types
- Associations between fear learning trajectories and personality traits were scant
- Findings tentatively support the fear-conditioning paradigm as a translational model

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