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Individual Differences in Associative Fear Learning
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Aims and scope

The objective of this dissertation was to gain a better understanding of individual differences in fear learning. While clinical studies have shown that following a traumatic event, individuals strongly differ in their vulnerability for or resilience to developing anxiety related disorders [21], this is often ignored in research and theory (e.g., [112,113,206]). As learned fear associations lie at the root of anxiety disorders [3], fear-conditioning is a widely used and successful laboratory paradigm for experimental research on anxiety [12,165,322]. Traditionally, studies focused on the acquisition of fear and tested average responding, which has provided highly valuable knowledge on fundamental fear-learning mechanisms. However, it can be questioned whether these general principles can be translated to real life anxiety, as abnormal development by definition implies a deviation from the norm. As such, individual differences may be central to reveal risk or resilient pathways of fear development [334]. There is a multitude of factors that determine risk for or resilience to anxiety, including individual differences in temperamental traits, biological variables, life history, and experiences during or after trauma (e.g. summarized by [206,283]). The current thesis focuses on personality variables.

To enhance insight in how normal fear evolves into abnormal fear, we integrated an individual differences approach with experimental fear-conditioning research [69]. For the experimental study of individual differences in fear processes in a controlled laboratory setting, our study designs combined methodologies for detecting individual variation, personality assessment, as well as extended fear-conditioning procedures. More specifically, we aimed to comprehensively uncover individual variation (heterogeneity) in fear learning. Additionally, we studied whether the distinct adaptive or maladaptive fear-learning trajectories resemble common response patterns to real-life threatening events, such as resilience, recovery, delayed fear or chronic anxiety [21,22,115]. In addition, we examined whether the individual variation in fear learning can be explained by variation in personality traits (e.g., [56]) and whether a dysfunctional emotional processing style (worry; [140]) can deteriorate associative fear and safety learning. To examine these questions, we specifically developed a series of human fear-conditioning experiments to examine heterogeneity in associative fear learning. We used different manipulations such as fear acquisition, extinction, generalization or reinstatement, and combined it with the assessment of risk and resilience traits or with a worry induction. Fear was measured as a multidimensional response including psychophysiological responses and subjective feelings [37,98,108], by distress ratings, startle fear responses (EMG), skin conductance (SCR) or shock (UCS) expectancy ratings.

With this research on individual differences in associative fear learning, we aimed to improve our understanding of mechanisms conferring vulnerability or resilience to anxiety. An overarching goal was to design the experiments to create optimal conditions for the expression of individual differences. Subsequently, the translational value of the fear-conditioning paradigm for understanding abnormal anxiety can be evaluated.

Summary of the results

Modeling individual differences in associative fear learning; the impact of worry on fear development

To enhance the applicability of the fear-conditioning paradigm for the study of individual differences we first developed a procedure to test the effect of one individual risk process in associative fear learning. Given that worrying is a key candidate in the development of anxiety [140]and that pathological fear may also evolve after a mild threat or without having been exposed to a (direct) threatening event (e.g., by receiving fear information; [73,101]), we questioned whether worry may contribute to maladaptive fear development. Therefore, in **Chapter 2**, we studied whether worrying can be experimentally manipulated and integrated within a fear-conditioning experiment. We hypothesized that worry would strengthen the fear association. It was tested whether experimentally induced worrying about feared outcomes by guided rehearsal of catastrophic statements on the personal consequences of a noxious event (i.e., the electric stimulus/shock) would lead to a dysfunctional persistence of fear responding. Our results indicated that a worry induction subsequent to fear conditioning can lead to an immediate elevation of the conditioned startle fear response and an impairment of extinction (only) at the cognitive level of conditioned responding (UCS expectancy). The finding that post-acquisition worrying affects the formation of fear memory can be explained by the principles of memory consolidation, which show that a memory trace can be changed after its original acquisition by either neurobiological or behavioural manipulations (e.g., [83,218]). In addition, the potential effects of worry on fear learning can reflect one way in which anxiety vulnerability traits confer their risk. This study also forms an example of how the fear-conditioning paradigm can be applied in healthy individuals to model maladaptive processes of anxiety.

Notwithstanding the interesting findings, a possible limitation of our design was that we cannot be certain whether the worry manipulation indeed induced worrying and whether this in turn 'caused' the differences in fear responding. Indeed, the difficulty of designing an appropriate manipulation check for a worry induction is acknowledged in the field (e.g., [145,329]). Moreover, some participants in the current study indicated that they failed to fully comply with the manipulation. Probably, for certain individuals it is difficult to engage in worry upon instruction, whereas others will habitually reflect on the aversive experience regardless of the instructions. Therefore, the alternative approach in the next experiments of **Chapter 3, 4 and 5** was to capitalize on existing differences in emotional processing styles that are likely present in individuals scoring high or low on relevant risk traits.

Heterogeneity in associative fear learning and the role of personality trait differences

We proceeded to further expand the fear-conditioning paradigm to model individual differences in fear learning. The next series of experiments tested the general hypothesis that

heterogeneity is evident in human fear conditioning. The main objectives of the next studies **in Chapter 3, 4 and 5** were threefold: a) to examine whether and how (ab)normalities in fear and safety learning could be detected, b) whether the different patterns resemble common fear development patterns in real life (e.g., [21]), and c) whether the different fear trajectories were related to existing differences in risk and resilience personality traits.

The study in **Chapter 3** was inspired by a discrepancy observed in the literature: while trait anxiety is a well-established risk factor for developing anxiety disorders (STAI-T; [122,155]), evidence for abnormal associative fear learning in high trait anxious (HTA) individuals is surprisingly scarce (see summary in Chapter 3 and [206]). If vulnerable and resilient individuals would not differ in fear conditioning, this would run counter to the alleged role of associative fear learning in the etiology as posited in human diathesis-stress models of anxiety disorders (e.g.,[12,217,234,336]). Hence, this would also limit the heuristic value of the fear-conditioning model for understanding individual differences and abnormal fear development. To overcome potential previous limitations in the scope and measures used to test fear learning, the experiment in **Chapter 3** compared a preselected group high on trait anxiety with a Control group (average on trait anxiety) in an extensive two-day course of fear learning and extinction, measuring multiple subjective and physiological indices of fear. In line with our predictions, HTA individuals showed stronger fear on the startle response and distress ratings to the safety stimulus (CS2–), but not to the threat stimulus (CS1+) during acquisition, along with impaired extinction and re-extinction. Further, UCS (shock) expectancy ratings also indicated deficient safety acquisition (CS2-) in HTA individuals. Thus, HTA participants displayed elevated fear responses to stimuli that were safe or no longer dangerous. Trait anxiety did not affect skin conductance responses. Our findings are largely in line with previously reported differences between anxiety patients and controls [85,201] and corroborated some previous findings in groups at risk (e.g., [67]), but were inconsistent with several reported null findings [257,267,316]. We conclude that high trait anxiety may be characterized by deficient safety learning, which in turn may promote persistent and overgeneralized fear responses.

The findings of **Chapter 3** provided general evidence for maladaptive fear learning in an at-risk group and thus supported the notion of heterogeneity in associative fear learning. These findings led us to proceed with the study of individual differences in fear-conditioning paradigms. While in Chapter 3 the study design allowed to test one broad risk trait, it is acknowledged that risk or resilience is determined by more than one trait and putative interactions between traits (e.g., [174,230,231,317]). In addition, it is plausible that multiple potentially adaptive or maladaptive patterns exist (e.g., [111,113]) and group averages may not reflect the pattern of an individual or subgroups (e.g., [171,206]). In the next part of this thesis, we focused on uncovering individual patterns of fear learning.

In the experiment described in **Chapter 4** we took a dimensional approach to investigate how variation in two selected personality risk traits predict variation in associative fear learning. Using multilevel growth curve modeling (MLM; [16,173]), we tested the hypotheses that a)

Stress Reaction and Harm Avoidance would show unique associations with fear conditioning and extinction and (b) the interactive effects of Stress Reaction and Harm Avoidance would be better predictors for fear-learning parameters than either trait in isolation. Our findings demonstrated weaker discrimination between threat and safety stimuli in terms of startle fear responses (EMG) in individuals high on Stress Reaction. Subsequently, both retention of differential fear acquisition and extinction were weaker with high levels of Stress Reaction and Harm Avoidance, thereby indicating maladaptive fear learning, whereas they were stronger with low levels of Stress Reaction and high levels of Harm Avoidance, suggesting efficient fear learning. These findings support the notion that the study of individual variation is useful to understand different mechanisms of fear learning [171]. Further, as the personality characteristics partly accounted for the identified distinct fear patterns, these trajectories present mechanisms of how traits may operate to confer risk for or resilience to anxiety.

The studies in **Chapter 3 and 4** provided further support for heterogeneity in fear learning, and yielded tentative relationships between variation in selected risk traits (or trait combinations) and variability in fear learning. It should be noted that the methodologies used were designed to test the predictive effect of personality traits (top-down), which allowed to uncover several trajectories. However, visual inspection of the raw data suggested a number of substantially different conditioning patterns (see e.g **Chapter 4**, Fig. 1 panel B). From clinical epidemiological work, we know that multiple fear patterns have been observed to real-life threat (e.g., [21,79,110]). These observations led to the idea of mapping the extant natural heterogeneity in fear learning. Such comprehensive identification of subpopulations is of potential relevance to understand the diversity and course of fear responses in real life. To develop the final study (**Chapter 5**), we further tailored the methodology to comprehensively examine heterogeneity in fear. In our previous chapters relatively homogeneous groups were tested (i.e., mostly students), which limits the diversity in fear learning as well as the generalizability to the general population. Given our objective to create the conditions for optimal testing of the translational value of the fear-conditioning model for understanding real life anxiety development, we assessed variability in fear learning in the general population. In addition, as most previous studies only focused on risk traits, to further explain variability in fear-learning we included a resilience trait that can protect against anxiety pathology (e.g., [317]).

Accordingly, **Chapter 5** describes a large-scale project that was set up to uncover variation in associative fear learning by studying a large heterogeneous representative sample (N=936). Instead of deciding (top-down) on how to combine the variables, we let the data govern the grouping of individuals in terms of similarity in fear learning, employing latent class growth modeling (LCGM; [241,243]). We investigated individual differences during the course of fear acquisition, extinction, generalization, reinstatement and re-extinction, while measuring subjective distress, startle responding (EMG) and skin conductance responding (SCR). Additionally, we examined whether these distinct patterns were characterized by differences in risk traits Harm Avoidance, Stress Reaction, and/or the resilience trait Wellbeing. We found that

seven subjective distress, five startle response (EMG), and four SCR trajectories provided the strongest model fits. Identified subpopulations included persons showing adaptive, intermediate, maladaptive, or limited-responding patterns. Notably, these trajectories largely resemble differential courses of real life fear development (e.g.,[21]). In addition, for subjective distress, maladaptive subgroups were -compared to the other classes- relatively high harmavoidant, adaptive subgroups were medium harmavoidant, and limited-responding subgroups were low on Harm Avoidance. However, distress subgroups showed only trend differences on Stress Reaction and were not characterized by differences in Wellbeing. In addition, no relationships between startle response (EMG) or SCR subgroups and personality were observed. The absence of relationships between the physiological patterns and personality and the smaller number of distinct physiological patterns may in part be related to the relatively large subgroups showing limited responsiveness. Together, findings in this final **Chapter 5** indicate that fear-learning patterns are heterogeneous, resemble risk and resilient anxiety development in real life, and provide tentative evidence that the strength of fear and safety learning on a subjective level is related to a personality risk trait.

In the General Discussion (**Chapter 6**) the main findings, implications, limitations and directions for future research are discussed. Our main findings show individual variation in associative fear learning on the four measured emotional response domains. These distinct courses of fear development ranged from adaptive to maladaptive and limited-responding trajectories, and also showed similarity to fear development in real life. We also found that variation in the fear trajectories was related to variation in anxiety risk traits. In addition, inducing worry, a key process of anxiety vulnerability, strengthened the initial formation of a fear association.

Our present results also allowed to answer which putative conditioning-related mechanisms were mostly involved in maladaptive fear learning: In summary, we found evidence for weak safety learning and extinction, but no evidence for the putative mechanism of 'enhanced fear learning' (without enhanced responding to other cues; see for details General Discussion). Furthermore, our findings revealed not only differences between individuals but also within-individual differences across phases. This indicates that the fear-learning process can turn (mal)adaptive in multiple ways and can be expressed at the start, end or across multiple phases. Hence, individuals can differ in their specific fear-conditioning-related weaknesses or strengths. In addition to these insights on the conditioning processes, the results on the four emotional response domains showed that variability was largest for subjective feelings of distress, for the startle fear response (EMG) larger than for the skin conductance response (SCR), and preliminary results suggest small variation in the shock expectation ratings. It may imply that distress ratings and startle responses are more suitable than SCR for understanding individual differences in (mal)adaptive fear development. A threatening stimulus elicits autonomic, behavioural and cognitive-emotional responses, and fear may thus best be conceptualized as 'a multidimensional response to danger'. Accordingly, assessment of these

multiple response domains, including both physiological measures and subjective distress reports, is essential to capturing fear, and most likely to advance knowledge on mechanisms of fear and its disorders [98].

The findings regarding the relationships between fear learning and personality should be interpreted with some caution. The associations between personality and fear-conditioning were limited and if present, of modest magnitude. Additionally, for the large-scale study in Chapter 5, the associations between the traits and fear conditioning were limited to outcome in terms of subjective distress and no relationship with the resilient personality trait appeared. We argue that the standard fear-conditioning experiment may not be optimally suited to elicit trait-relevant responding. For example, only minimal opportunities for avoidance behaviour are provided and the "dosing" of the stress associated with the mild experimental shocks may not adequately trigger individual differences in Stress Reaction. Future research is required to obtain more conclusive results. That said, although the effects of personality of fear conditioning were generally small to modest, they may reflect meaningful relationships, as they were largely in line with our hypotheses based on both theoretical (e.g., [12,314]), and clinical work (e.g., [110,174,230,231]). One explanation that may account for the lack of associations in Chapter 5 concerns our analytic strategy: by collapsing all learning phases (i.e., acquisition, extinction, generalization etc.) we may have obscured phase-specific trait associations (which may exist in one phase, but not in another, or even counter balance). Alternatively, it can be speculated that vulnerability and resilient traits exert their effects more strongly through other pathways than direct fear conditioning (e.g., avoidance conditioning, emotion regulation). Another limitation of Chapter 5 was that a relatively large proportion of the samples showed limited responses on the physiological measures (limited responders). Certain aspects of the fear-conditioning procedures or physiological measurements, which have been extensively tested and developed in relatively homogeneous groups, may not have been optimally suited for a representative and thus more heterogeneous sample.

Based on our findings, a number of potential implications for understanding vulnerability to clinical anxiety or for future improvement of interventions can be suggested. The observations that fear learning can turn maladaptive or adaptive in many ways and at different phases provide indications on how and by which process anxiety development can go awry. This also implies that there are probably different 'vulnerable' and 'resilient' subtypes of fear learning. An area for future research could be to test the predictive validity of associative fear learning. One could test whether these maladaptive or adaptive patterns predict the development of anxiety symptoms or anxiety disorders in the long term, and whether specific fear-learning impairments predict different subtypes of anxiety symptomatology. Continuing this bold speculation with respect to clinical applications, it is conceivable that distinct fear-learning subtypes would benefit from different preventive or treatment interventions or may differentially predict treatment efficacy. To execute such studies, research is also needed into methods for predicting heterogeneous responses to potentially traumatic events based on deviations

in associative fear learning. A translational approach integrating fear conditioning with (sub) clinical research and advanced methodologies offers an experimental framework in which these predictions can be tested.

Conclusion

The studies in this thesis presented evidence for heterogeneity in human associative fear learning. Though it is self-evident that the experimental models used in this thesis are an oversimplification of real-life fear development, the different fear trajectories still provide indications for potentially adaptive and maladaptive fear-learning mechanisms. The current findings partly support the utility of the fear-conditioning paradigm as a translational model for understanding anxiety disorders. We used novel methodological and analytical approaches that may provide inspiration for further study of 'intermediate phenotypes' that underscore maladaptive fear learning. Advancing knowledge on the diverse courses of fear learning and its determinants may foster our understanding of anxiety-related disorders and sharpen future targets for improving clinical interventions