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Review article

More than just noise: Inter-individual differences in fear acquisition, extinction and return of fear in humans - Biological, experiential, temperamental factors, and methodological pitfalls

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ABSTRACT

Why do only some individuals develop pathological anxiety following adverse events? Fear acquisition, extinction and return of fear paradigms serve as experimental learning models for the development, treatment and relapse of anxiety. Individual differences in experimental performance were however mostly regarded as '*noise*' by researchers interested in basic associative learning principles. Our work for the first time presents a comprehensive literature overview and methodological discussion on inter-individual differences in fear acquisition, extinction and return of fear. We tell a story from noise that steadily develops into a meaningful tune and converges to a model of mechanisms contributing to individual risk/resilience with respect to fear and anxiety-related behavior. Furthermore, in light of the present 'replicability crisis' we identify methodological pitfalls and provide suggestions for study design and analyses tailored to individual difference research in fear conditioning. Ultimately, synergistic transdisciplinary and collaborative efforts hold promise to not only improve our mechanistic understanding but can also be expected to contribute to the development of specifically tailored ('individualized') intervention and targeted prevention programs in the future.

Why do some individuals develop pathological anxiety in the aftermath of trauma while others do not? Why do some patients profit from treatment while others do not? On the one hand, exposure to a traumatic event is clearly not sufficient for the development of anxiety or trauma- and stressor-related disorders (e.g., (Bonanno, 2004)). On the other hand, the generally best treatment option ('one size fits all') is not suitable for every patient (e.g., Ozomaro et al., 2013). Such differences in vulnerability and reactivity are strongly related to inter-individual differences with respect to their life history before, during and after trauma (experiential differences) as well as biological and/or temperamental factors (i.e. trait variables) – all of which strongly interact.

Similarly, in experimental situations, pronounced inter-individual differences in fear and anxiety-related responding are observed despite completely identical procedures (see 1.1). Hence, experimental studies on inter-individual differences may provide critical insights into the mechanisms underlying divergent responses in the aftermath of traumatic experiences and individual risk factors and trajectories for the development of anxiety and/or stress-related disorders (Mineka and Oehlberg, 2008). Ultimately, this endeavor may help to pinpoint factors conferring differential vulnerability to psychopathology or conveying resilience and may inform the development of targeted prevention and intervention programs tailored to the individual and/or at-risk groups (for a discussion see Insel, 2014).

We set out by providing a brief introduction into fear conditioning as a clinically highly relevant model for studying acquisition, treatment and relapse of fear and anxiety (see Section 1). We then outline a current paradigm shift from the study of average responding towards the appreciation of the role and opportunities of inter-individual differences in fear conditioning processes (see Section 1.1). This leads over to a discussion on critical design and analyses considerations and recommendations (see Section 2) which are of crucial importance for our narrative review of biological, experiential (see Section 3) and temperamental factors (see Section 4) in fear conditioning research in healthy humans which represents the centerpiece of this work.

Prior to going into detail, it is useful to define the term 'individual

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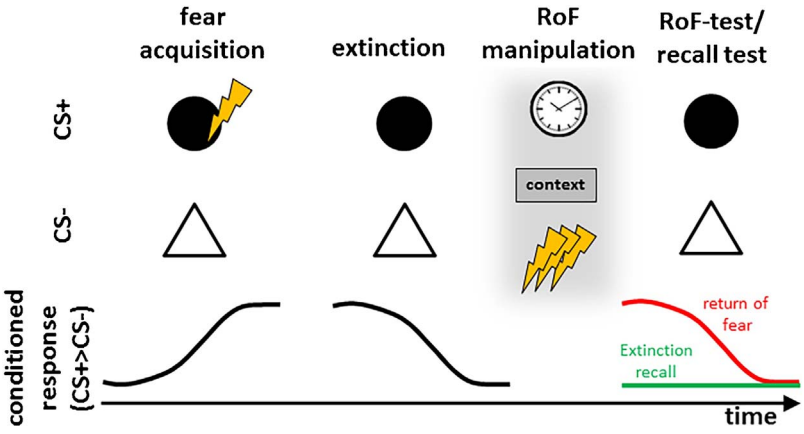

Fig. 1. Experimental phases of a differential fear conditioning experiment encompassing fear acquisition, extinction, return of fear (RoF) manipulation and RoF-test/recall test (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
The black circle serves as conditioned stimulus (CS+) paired with the aversive unconditioned stimulus (bolt) only during fear acquisition, whereas the white triangle is not paired (CS-). The development and extinction of conditioned responding (i.e. higher responses towards the CS+ compared to the CS- changing over time) are displayed with black lines. Note that the clock indicates passing of time leading to spontaneous recovery, the 'context' icon indicates contextual change between extinction and RoF-test leading to renewal and the bolts indicate reinstatement-USs to provoke reinstatement-induced RoF. Also note that extinction recall and RoF-test, in particular with respect to spontaneous recovery, do not differ procedurally but can only be differentiated conceptually by the prediction of the dominant memory trace at test (i.e. fear or extinction memory dominance leading to expression of conditioned responding at test [red line] or not [green line] respectively) or the observation of return of conditioned responding [red line, RoF] or not [green line, extinction recall].

differences', as conceptualized in general and in the specific context of this work. Research on individual differences, an aspect of psychology termed 'differential psychology', studies the ways in which individuals differ in their characteristics, their behavior as well as the underlying processes. Thereby, individual differences can refer to 1) differences between individuals (*inter-individual differences)*, 2) differences within the same person over time (*intra-individual differences*) as well as 3) differences between individuals with respect to changes over time within one person (*inter-individual differences of intra-individual differences;* i.e., trajectories).

The present work provides an overview on inter-individual differences in fear conditioning, as this has been the main focus of research in the field to date. Although highly relevant, intra-individual differences as well as inter-individual differences in intra-individual differences have been rarely investigated as of yet and are therefore not included.

Despite a plethora of studies, the field of inter-individual differences in fear acquisition, extinction and return of fear processes lacks a systematic and comprehensive narrative review of the literature as well as a methodological discussion, a challenge that has been taken up by members of the '*Research Network for the European Interdisciplinary Study of Fear and Extinction Learning as well as the Return of Fear (EIFEL-ROF)'* in the present work. Arguably, a *comparative* work including both healthy and patient samples would align with the conceptualization of pathological fear and anxiety as one end of the continuum as implemented in the Research Domain Criteria (RDoC) approach (for a discussion see Insel, 2014). While a comprehensive in-depth review and meta-analytic data are already available for results in clinical samples (for meta-analyses see Duits et al., 2015; Lissek et al., 2005), an overview on the plethora of results in *healthy samples* as well as a systematic investigation with respect to the experimentally derived inter-individual difference factors is however currently lacking. Hence, for reasons of space restrictions and methodologically (partly) divergent approaches, we here focus on work on healthy participants but refer to results in or applications for clinical populations when appropriate – however without an in-depth discussion.

1. Fear acquisition, extinction and return of fear as experimental models

The development, treatment and relapse of anxiety, trauma- and stressor-related disorders can be modelled experimentally by employing fear conditioning paradigms including acquisition, extinction and the return of fear (Mineka and Oehlberg, 2008; Milad and Quirk, 2012; Mineka and Zinbarg, 2006; Vervliet et al., 2013a). In the following, 'fear conditioning' will be used as an umbrella term subsuming fear acquisition, extinction and return of fear procedures (see Lonsdorf et al., 2017), which will be introduced in brief.

Fear acquisition imbues a relatively neutral stimulus (the to-be conditioned stimulus, CS; also referred to as 'conditional stimulus') with fear-evoking properties as the result of its co-occurrence with an aversive event (the unconditioned stimulus, US; also referred to as 'unconditional stimulus') threatening the well-being of the organism. In cognitive terms, the organism learns that the CS is a reliable predictor of the dangerous US (which may also occur through observation or instruction), evokes anticipatory (fear) reactions and mobilizes defensive reaction mechanisms (i.e. conditioned responses, CRs; also referred to as conditional responses). In human work, these CRs are commonly assessed as skin conductance responses (SCRs), fear potentiated startle responses (FPS), ratings of fear and US-expectancy or neural activation patterns. Of note, these different outcome measures capture partly distinct processes (for a discussion see Lonsdorf et al., 2017).

Importantly, a clear distinction exists between fear- and anxiety-related processes. Whereas *fear* represents the response to a specific, stimulus-driven threat ('phasic') at a specific point in time, *anxiety* represents a sustained and more general state of distress towards future threats and challenges which can be elicited by more generalized or less explicit stimuli (cf. Davis, 1998; Davis et al., 2010; Lang et al., 2000).

Notably, fear conditioning plays a key role in psychological theories of anxiety disorders such as phobias (Ohman and Mineka, 2001; Seligman, 1971), panic disorder (Bouton et al., 2001), as well as post-traumatic stress disorder (PTSD) (Orr et al., 2000). The theoretical constructs of *fear* and *anxiety* are thought to have their parallels in human psychopathology with some anxiety and trauma- and stressor-related disorders linked to phasic fear (e.g. phobias, PTSD) while others are linked to sustained anxiety (e.g. generalized anxiety disorder, panic disorder). Notably, corresponding procedural variations (cue vs. context conditioning) have been developed to test these different states (Baas et al., 2004; Grillon, 2002a; Grillon et al., 2006).

Fear acquisition protocols (a procedure referred to as acquisition training; Lonsdorf et al., 2017) in humans typically employ *differential* protocols, in which one CS (CS+) is predictive of the US, while a second one is not (CS-; see Fig. 1). Differential conditioning, which is most commonly employed in human work, involves excitatory learning to the CS+ as well as (at least under certain circumstances such as perceptual similarity and contextual conditioning) inhibitory learning to the CS-, which signals the absence of danger ('safety stimulus'). Note that the CS- was initially included for methodological reasons, there is increasing interest in the 'safety' properties of this cue in the recent past. Conditioned responding, reflective of fear expression, in autonomic, neural, verbal and/or behavioral reactions is quantified as the difference in response amplitude/strength to the CS+ as compared to the CS- that may derive from either differences in excitatory (i.e., CS+ responding) or inhibitory (i.e., CS- responding) processes. Note however that response differences to the CS- may also derive from