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
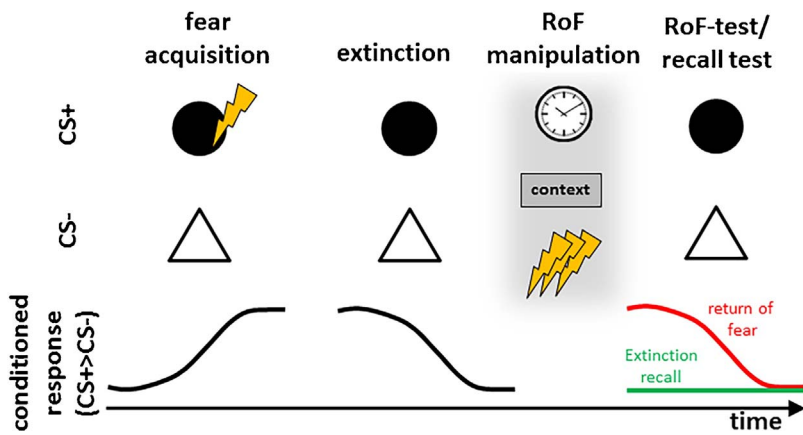
development of anxiety and/or stress-related disorders (Mineka and Oehlberg, 2008). Ultimately, this endeavor may help to pinpoint factors conferring differential vulnerability to psychopathology or conveying resilience and may inform the development of targeted prevention and intervention programs tailored 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

differences in perceptual similarity between CS+/CS- discrimination or differences in contextual conditioning (or combinations thereof). In sum, fear acquisition has been established as an outstanding, valid and widely used translational model for the experimental investigation of mechanisms underlying pathological fear and anxiety (Milad and Quirk, 2012; Vervliet and Raes, 2013).

In changing environments, responding has to be adapted constantly to initiate adequate behavior. For instance, when a previously threatening stimulus has lost its predictive power, defensive responding towards this stimulus will cease. Hence, the presentation of unreinforced CS+ presentations (a procedure referred to as extinction training; Lonsdorf et al., 2017) leads to a gradual waning of (differential; i.e. CS + > CS-) conditioned responding, a process referred to as *extinction* (see Fig. 1). Notably, extinction does not lead to erasure of the excitatory fear memory trace (i.e. CS-US association) under most circumstances. In most cases, extinction generates a competing CS-noUS association which serves to inhibit the activation of the fear memory. Hence, following successful extinction training, a fear-inhibitory extinction memory trace (CS-no US association) is thought to co-exist with the fear memory trace (Bouton, 2004; Myers and Davis, 2007). Importantly, the procedure and effect of extinction training have obvious implications for the treatment of anxiety disorders (Milad and Quirk, 2012; Anderson and Insel, 2006) and inspired highly efficient exposure treatments (Barlow, 2002). For a (partly) critical discussion on the validity of extinction protocols for exposure-based treatment and a discussion on empirical evidence we refer to Scheveneels et al., (2016).

Resulting from the above and depending on the dominance of one of these memory traces over the other, fear may return after successful extinction (see Fig. 1). Indeed, high relapse rates after initial treatment success represent a major limitation to long-term remission of anxiety disorders despite effective psychological and pharmacological interventions (Yonkers et al., 2003). Advancing the understanding of clinical relapse may thus provide a first step towards improvement in long-term remission.

Relapses can be modelled in experimental fear conditioning paradigms through so-called *return of fear* procedures following (successful) extinction training (see Fig. 1), the validity of which have recently been discussed (Scheveneels et al., 2016). Experimental procedures encompass the mere passage of time (*spontaneous recovery*), induction of contextual change (*renewal*) or exposure to unsignaled USs (*reinstatement*; Bouton, 2002, Vervliet et al., 2013b; Haaker et al., 2014). Different return of fear phenomena are thought to model different clinical mechanisms underlying clinical relapse (or at least resurgence of fear) such as insufficient generalization of safety learning from the safe therapeutic situation to every-day situations (renewal; Vervliet et al., 2013a) or relapse following exposure to life adversity (Scharfenort et al., 2016).

Indeed, results from clinical samples also inspire further developments in basic fear conditioning research and vice versa. In order to understand how specific (combinations of) inter-individual difference factors in fear acquisition, extinction and return of fear might be related to psychopathology, findings derived from patient studies need to be briefly considered. To give a few examples, impaired safety signal processing or increased fear generalization has been proposed in patients with panic disorder, since enhanced CRs were found towards the CS- during fear acquisition (Lissek et al., 2009; Lueken et al., 2014). Additionally, patients with panic disorder exerted increased CRs towards the CS+ indicating facilitated processing of danger cues (Michael et al., 2007). In patients with specific phobia, enhanced differential (i.e. CS + > CS-) CRs have been observed during fear acquisition, in particular towards phobia-specific US (Schweckendiek et al., 2011; Vriends et al., 2012). During early fear acquisition and extinction recall, a reduced differential activation of the inhibitory-related ventromedial prefrontal cortex (vmPFC) has been observed across different anxiety disorders, which was also associated with heightened symptom severity (Marin et al., 2017). Likewise, patients with PTSD

exerted this hypoactivation of the vmPFC among others during extinction recall (Milad et al., 2009a) as well as enhanced general responding to the CS and increased CS+/CS- differentiation during fear acquisition (Orr et al., 2000; Norrholm et al., 2011) and delayed extinction (Norrholm et al., 2011; Blechert et al., 2007; Peri et al., 2000) when compared with trauma-exposed or healthy controls. For a comparison between these mental disorders and further details concerning altered fear conditioning processes in other mental disorders, we refer the interested reader to a recent review (Nees et al., 2015) and related meta-analyses (Duits et al., 2015; Lissek et al., 2005).

1.1. Signals in the noise: a paradigm shift from average responding to a focus on inter-individual differences

Fear conditioning rapidly became an epitome of learning and environmentalism in the 20th century. Even though inter-individual differences in acquisition and extinction have already been described by Pavlov in 1927 (Pavlov, 1927), research focused on average responding for decades, which enabled establishing and studying the basic and universal principles of (aversive) associative learning. While crucially important, this came at the cost of individual differences, which were regarded as 'noise' and 'unexplained variance' ('average responding') in the context of this experimental work. Consequently, the general neural, behavioral and physiological underpinnings of and mechanisms underlying fear conditioning are today well established in both rodents and humans (Milad and Quirk, 2012; Fullana et al., 2015; Kim and Jung, 2006; LeDoux, 2000; Maren, 2001) providing the base for the investigation of individual differences therein.

A limited focus on average responding and treating variance in data as 'noise' rather than data (Kosslyn et al., 2002), however, deprives us from gaining crucial insights into fear conditioning processes beyond the average, which has recently been recognized also by rodent researchers (Ardi et al., 2016; Bush et al., 2007; Galatzer-Levy et al., 2013, 2017). That is, group analyses do not necessarily provide meaningful information about potential subgroups and similarly, comparisons between subgroup means do not necessarily provide meaningful information about the individual. For instance, the absence of significant differences in responding to a threat and a danger signal (i.e. type II error) in the group as a whole may result from the existence of two subpopulations within a given study sample exhibiting opposite response patterns (e.g. one subpopulation showing higher responding to the CS + than to the CS- and one subpopulation showing higher responding to the CS- than to the CS+) despite identical procedural conditions. The same argument applies to activation in a certain brain region in a specific task: Task-related effects might not be revealed in presence of substantial variation across individuals in the strength of recruiting this area or even in the activation pattern across areas. Hence, the existence of unrecognized subpopulations may obscure important response patterns. As a matter of fact, the sample mean may not describe responding of any individual very well and may not necessarily translate into useful information for subgroups of patients ('one size fits none' rather than 'one size fits all'). In addition, individual response trajectories (Bonanno, 2004, 2012; Galatzer-Levy et al., 2013, 2017) may provide additional valuable information beyond subgroup mean responses. As such, the study of average responding and individual differences between subgroups of individuals (Sauce and Matzel, 2013) as well as analyses of individual response trajectories (over time) need to form a synergy to mutually inform our understanding of fear conditioning processes and their underlying mechanisms to ultimately allow translation of these findings to the clinics (see Section 2.2 for discussion on methods for research on individual differences). Complementary, single case designs might be considered as a third approach also providing critical insights into the transition from an extreme manifestation of a special inter-individual difference factor to psychopathological problems and the underlying mechanisms. To date, only a limited number of publications is available investigating fear

conditioning processes in single case reports (Bechara et al., 1995; Heutink et al., 2011; Klumpers et al., 2015a; for larger groups of neuropsychiatric patients see LaBar et al., 1995; Weike et al., 2005).

This is particularly relevant as only a small fraction of individuals exposed to a traumatic event will develop PTSD (Breslau et al., 2004) while other show resistance or recovery (Bonanno, 2004). Similarly, only a fraction of patients will respond favorably to treatment and an even smaller fraction will show long-term remission (Yonkers et al., 2003). Let's think about an example: an inter-individual difference factor X predisposing to exaggerated fear acquisition will likely not have long-term consequences when co-occurring with the inter-individual difference factor Y predisposing to rapid or facilitated extinction learning. In contrast, when X is combined with the inter-individual difference factor Z predisposing towards delayed or impaired extinction learning, exaggerated (pathological) fear or anxiety may result. Hence, it is of fundamental importance to uncover factors, and particularly their interaction, contributing to individual differences in the vulnerability to pathological fear and anxiety (the X and Z) as well as to resilience (the Y) in order to develop individually tailored prevention and intervention programs ('precision medicine'), which are already widely employed in other disciplines such as oncology (e.g., Insel, 2014; Rodríguez-Antona and Taron, 2015).

Inter-individual differences in fear conditioning research first gained interest in the human field in the 1950s and the 1980s (for a review see Levey and Martin, 1981; Zinbarg and Mohlman, 1998). But it was not before the past decade that the key importance of inter-individual differences has also been recognized in animal research (Bush et al., 2007; Galatzer-Levy et al., 2013; Galatzer-Levy et al., 2017; Driscoll et al., 2009). In the present narrative review, we focus mainly on the more recent literature in humans without giving a detailed historical perspective for reasons of space and as the limited number of very early studies in the field used different procedural and methodological approaches. As the field we review has nearly exclusively relied on measures of central tendencies we provide a brief outline on this and alternative methodological approaches in Section 2.2.

The in-depth compilation of the current state-of-the-art in experimental work we provide here is reflective of an ongoing paradigm shift from a previous focus on average responding uncovering *general mechanisms* of fear acquisition, extinction and return of fear to a strengthened focus on individual difference factors (Bonanno, 2004, 2005, 2012; Galatzer-Levy et al., 2013, 2017; Gazendam et al., 2014), which is evident from the increasing number of publications on individual differences in fear conditioning research. Anxiety as well as trauma- and stressor-related disorders are highly prevalent, costly and deliberating conditions. Thus, there is an imperative need to identify early risk, but also resilience factors in experimental pre-clinical approaches in order to aid development of timely and individually tailored prevention and intervention programs for groups and individuals at risk. As such, inter-individual difference factors influencing relative risk in laboratory models hold promise to advance our understanding and ultimately lead to improved treatments. In general, this approach calls for systematic investigations linking inter-individual differences in experimental fear conditioning performance (i.e., fear acquisition, extinction, return of fear) to clinically relevant variables (i.e., symptom severity, disease risk, treatment outcome, relapse risk). Admittedly, studies addressing this question of predictive validity as well as providing empirical evidence for extinction learning as the underlying mechanism of exposure therapy are sparse to date (Scheveneels et al., 2016).

Overall, a number of inter-individual difference factors linked to experimental fear conditioning processes have been identified, which can be largely grouped into biological, experiential (see Section 3) and (see Section 4) temperamental factors, although these categories are inherently intertwined. Owing to the recentness of the ongoing paradigm shift and the infancy of the field of inter-individual differences in fear conditioning research, the available evidence does not always

allow for crystal clear conclusions. Despite a seemingly large number of studies on individual differences in fear conditioning research in general (which are included in this narrative review; N = 120) and which were published primarily in the past 10–15 years), available work on specific individual difference factors is limited and has not been pursued systematically. A comprehensive compilation of the available evidence together with the discussion of limitations, methodological considerations and suggestions and open questions however can nevertheless be expected to provide a fruitful input for the future of the field (i.e., reducing noise in favor of the signal). Before summarizing findings in the recent experimental literature in humans however, we provide a compilation of different procedural and data analysis considerations that we consider of paramount importance in inter-individual differences research in fear conditioning. This methodological discussion is meant to establish groundwork for putting the subsequently provided narrative literature review into perspective and justifies as well as aids interpretation of findings by directing the reader's attention to these important methodological details.

1.2. Search method

The goal of our narrative review was to provide a comprehensive overview of the field of inter-individual differences in fear conditioning, extinction and return of fear research that converges to a descriptive model of mechanisms contributing to individual risk and resilience (see Section 5) with respect to fear and anxiety-related behaviors. Accordingly, our narrative review includes 120 citations covering the period between 1991 and 2016 with most of the work representing recent research published within the past decade (publications 'in press' were coded as 2016). Importantly, the presented results might be subject to publication bias meaning that positive findings are more likely to be reported than negative findings. Consequently, the overall picture concerning the contribution of a specific individual difference factor on different fear conditioning processes could be less clear than anticipated. In this narrative review, we focus on healthy populations but provide a bridge to evidence from studies in psychiatric patients and in animals where appropriate. Importantly, our work brings together original work and reviews from a broad spectrum of disciplines such as psychology (developmental, differential, biological, clinical), neuroscience, genetics, endocrinology as well as psychiatry providing a comprehensive picture that may serve as a departure-point and guide for future work.

A Pubmed search was performed for the terms 'fear conditioning', 'extinction' and 'return of fear' in combination with different inter-individual difference factors as listed in the list of contents (i.e., age, sex hormones/differences, brain morphometry, cortisol, life events, trait anxiety, state anxiety, neuroticism, intolerance of uncertainty). Publications merely including animal work, clinical samples, targeting intra-individual differences (e.g., sleep deprivation) or eyeblink conditioning studies were excluded. Identified articles were screened for additional references of relevance to increase coverage. The Pubmed search was repeated in a final check-up on December 20th 2016. Data on inter-individual difference factors will be summarized below, grouped within a broader framework of biological, experiential and temperamental factors and presented separately for fear acquisition, extinction and return of fear whenever possible.

2. Procedural and data analysis considerations for inter-individual differences research in fear conditioning

Already Eysenck (1967) noted that the impact of inter-individual differences (i.e., personality traits) on fear conditioning performance critically depend on procedural specifics (see Section 2.1). The consideration of important procedural and data analysis details is of utmost importance not only to the interpretation of findings that will be reviewed herein, but is also highly relevant in light of the present

discussion on the 'replicability crisis in psychology' (Open Science Collaboration, 2015; Open Science Collaboration, 2012; Stroebe and Strack, 2014). More precisely, the impact of apparently subtle but powerful procedural differences across studies may tip the balance towards the manifestation of inter-individual differences or not – in particular as studies pursuing an individual differences approach often deal with comparably small effect sizes. Furthermore, unintended differences in sample characteristics across studies beyond the variable(s) of interest may lead to replicability issues. Hence, both factors may act as boundary conditions of a specific phenomenon, such as fear acquisition or fear extinction performance. More precisely, procedural and sample characteristics may gate or hamper the manifestation of (individual differences in) a certain phenomenon. As such, systematic investigations of replication failures may potentially inform us about such boundary conditions, which might be facilitated through the adoption of pre-registration of study plans. To advance this line of argumentation, Supplementary Table 1 provides an overview on sample characteristics, operationalization of inter-individual differences and outcome measures whereas Supplementary Table 2 provides an overview of procedural details of studies included in this narrative review.

In the following, we provide a non-exhaustive exemplary compilation of factors that may significantly impact on whether inter-individual differences manifest themselves in task performance of fear conditioning experiments or not. Importantly, these factors need to be carefully considered in the design of future studies on inter-individual differences in fear conditioning research and interpretation of the literature, which is contingent upon detailed methods descriptions in publications (see Lonsdorf et al., 2017 for a checklist and recommendations on what details to include in publications). Supplementary Table 1 and 2 and the factors listed there may thereby also serve as a guide and checklist on what factors should be included in scientific reports on inter-individual differences in fear conditioning, which hopefully will promote replication and interpretation of apparent non-replications and ultimately contribute to the reduction of noise in favor of the signal

2.1. Procedural factors

2.1.1. The 'strong experimental situation'

Experimental protocols can either induce strong (simple/predictable/certain) or weak (complex/uncertain/ambiguous) situations, based on specific characteristics of the procedure such as reinforcement ratio (i.e., frequency of CS + /US pairings during fear acquisition), instructions or number of CSs etc. (Lonsdorf et al., 2017; Beckers et al., 2013; Lissek et al., 2006). These factors are hence compiled for the studies included in this narrative review in Supplementary Table 2.

Lissek et al. (2006) convincingly argue that particularly weak situations (e.g., low reinforcement ratio) may theoretically allow for the manifestation of inter-individual differences, whereas strong situations (e.g., high reinforcement ratio) can be expected to induce rather uniform responding across participants. They thus recommend that research targeting inter-individual differences in fear conditioning processes should employ experimental designs that reduce the potency of the situation to increase the likelihood of detecting differential response thresholds. This has however not yet been tested empirically to our knowledge. Alternatively, it can also be speculated that the strength of the experimental situation *interacts* with inter-individual differences factors (see Section 4.1. for an example) in that certain individual difference factors manifest their impact only or primarily under different situational demands (e.g., factor X may only play a role in 'weak' situations while factor Y may only play a role in 'strong' situations) or that the impact of a certain individual difference factor differs in quality depending on situational demands (e.g., in 'weak' situations, factor Z may impact on CS- responding while the same factor Z impacts on CS + responding in 'strong' situations). Fig. 2A exemplarily illustrates the reinforcement ratio (as derived from Supplementary Table 2) employed

in individual difference studies on fear conditioning illustrating the abundance of high reinforcement ratios in the field.

2.1.2. Characteristics of the stimulus material

Special attention needs to be addressed to the selection of appropriate stimulus material (i.e., CS, US type) for inter-individual difference research in fear conditioning. More precisely, identical stimuli might be differentially salient or aversive for different biologically-based subpopulations (e.g., age-cohorts, sexes) or simply based on previous experience (e.g., existing life adversity, disorder-relevant CSs or USs, in-group vs. out-group CS, pre-exposure to the CS or US). As stimulus salience strongly impacts on fear conditioning performance (for a discussion see Lonsdorf et al., 2017), *unintended* differences in pre-experimental responsivity to stimulus material across groups may severely influence results. Detailed information on stimulus material employed across studies investigating inter-individual differences in fear conditioning is listed in Supplementary Table 2.

2.1.3. Diversity of read-out measures

Importantly, different read-out measures of CRs (such as SCRs, FPS, ratings or neural activation) may (partly) tap into slightly different underlying mechanisms (Lonsdorf et al., 2017). Consequently, different read-out measures may display different levels of penetrance with respect to commonly subtle inter-individual differences in fear conditioning processes. To allow to easily capture the frequency at which different read-out measures are employed in the field of inter-individual differences in fear conditioning, comprehensive information with regards to this can be found in Supplementary Table 1.

Based on different measures capturing partly different processes, a multimethodological approach across units of analyses, possibly extending common measures to measures of avoidance or instrumental behavior (Scheveneels et al., 2016) and defensive immobility (e.g., freezing as assessed by Roelofs et al., 2017; Volcan et al. 2017) which are not commonly employed yet, seem advantageous to shed light on inter-individual differences in fear conditioning, extinction and return of fear. In particular, strengthening research on (individual differences in) avoidance as a key diagnostic feature in anxiety disorders (e.g., Krypotos et al., 2015) can be expected to be highly important for theoretical and clinical reasons.

Furthermore, between-subject variation is substantial in physiological measures, but seems to be somewhat smaller for verbal measures of conditioned fear (Torrents-Rodas et al., 2014). Thus, selection of appropriate read-out measures for inter-individual difference research inherently relies on the ability to capture (subtle) variance in responding.

Relatedly, not specific to inter-individual differences research, statistical results and discussion of findings need to be characterized by sufficient specificity of reporting with respect to the read-out measure. More precisely, to promote clarity and enable easy comparability across studies, it should be explicitly stated which effect was observed in which read-out measure or not (e.g. 'high trait anxiety was linked to differential fear conditioning in SCRs and ratings of US expectancy, but not in FPS'). Undifferentiated and therefore ambiguous statements (e.g., '[higher] trait anxiety was linked to [differential] fear conditioning') should be avoided. This should be recognized not only in the results sections of publications but also in all other parts of reports (i.e., introduction, discussion, abstract).

2.1.4. Recruitment strategies and sample size calculations

It is well-known that participants in psychological experiments often represent student samples (Henrich et al., 2010). This is confirmed by a compilation of recruitment strategies employed in inter-individual difference research in fear conditioning (illustrated in Fig. 2B and C and listed in detail in Supplementary Table 1). This may be particular problematic in research on inter-individual difference variables as results may not necessarily translate to the general population
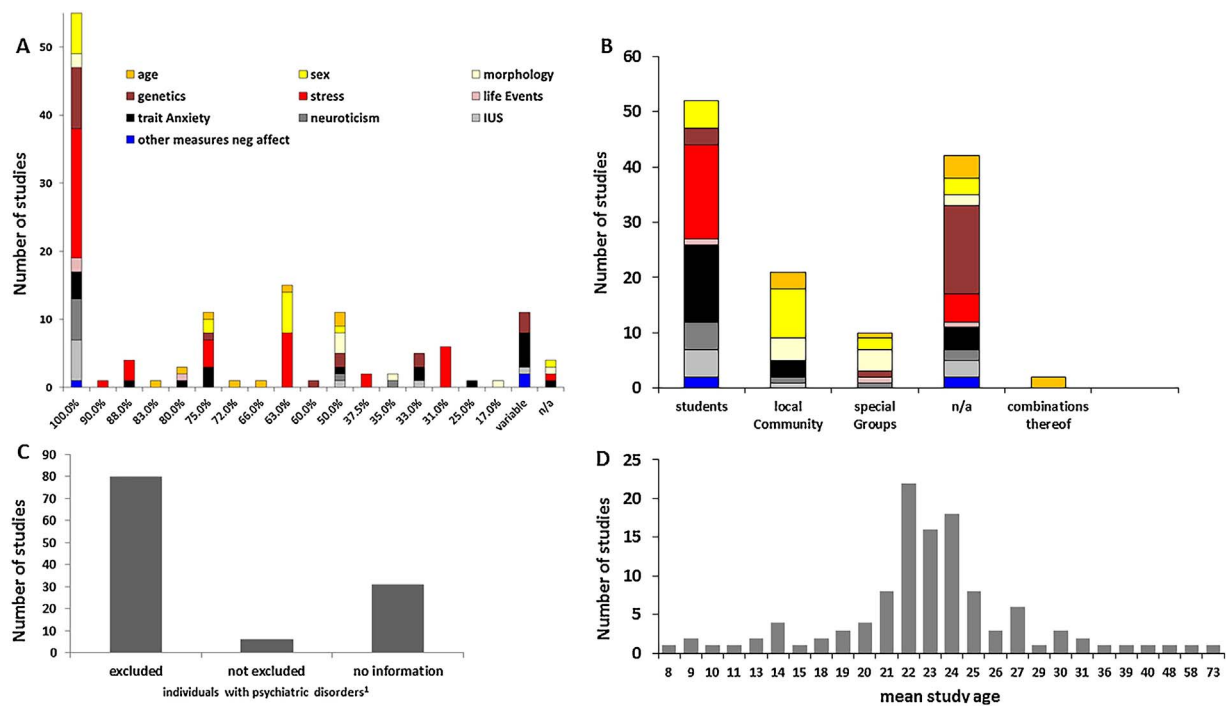
Fig. 2. (A) Exemplary illustration of the number of studies on inter-individual differences in fear conditioning employing different reinforcement ratios (rounded up) across inter-individual difference factors (as derived from Supplementary Table 2). Illustration of (B) treatment of individuals with mental disorders across studies[1] and (C) recruitment strategies in individual difference research in fear conditioning. n/a indicates that no information was provided in the publication. Generally, two studies reported within a single publication are considered as two separate studies for the purpose of this figure. (D) Illustration of mean age across studies on individual differences in fear conditioning (note that studies reporting only subsample mean values, these values were averaged except for studies on age in which subgroups are displayed individually).

[1]Note that exclusion of participants with mental disorders was partly based on clinical diagnostic interviews or participants' self-reports as well as lifetime and/or current conditions or based on intake of psychotropic medication. Furthermore, studies were counted as 'did not exclude participants with mental disorders' if exclusion criteria in general were listed without mentioning mental disorders, whereas studies listed as 'provided no information' did not list any exclusion criteria.

or across studies due to sampling bias. For instance, it becomes evident that most of the results and conclusions in the field are based on samples aged 22–25 years − likely due to recruitment from student populations. Hence, it is currently unclear how results on individual differences in fear conditioning research can be translated to other age groups represented much less abundantly (e.g., particularly individuals aged 30 +). As a consequence, advantages and disadvantages of the recruitment of 'convenience samples' (student samples) should be carefully considered and adequately taken into account in the interpretation of results.

In addition, studies differ with respect to the exclusion of participants with current or lifetime psychiatric diagnoses, which may potentially bias results. As recruiting strategy may massively bias results, studies need to report procedures in detail, which is not yet standard as evident from Figs. 2 B and 1 C (as indicated by n/a). In addition to the clustering of recruitment strategies for specific individual difference factors, few studies have employed *a-priori* sample size calculations − likely owing to the oftentimes exploratory or post-hoc nature of analysis and the lack of available data on effect sizes. Future studies should carefully consider recruitment strategies and their potential impact on the results as well as motivate selected sample sizes.

2.1.5. Test-retest reliability

Individual difference research critically depends on the reliable and reproducible quantification of conditioning performance over time (i.e. *test-retest reliability*), in particular research focusing on intra-individual differences. Even though this narrative review focuses on between-subject differences, this topic is important to keep in mind. With respect to fear conditioning, within-subject reproducibility and test-retest reliability has been established for conditioned SCRs across time intervals ranging from three weeks to eight months (eight months: Torrents-Rodas et al., 2014, three weeks: Fredrikson et al., 1993, eight to twelve

weeks: Zeidan et al., 2012).

Furthermore, temporal stability has also been reported for differential FPS as well as for US expectancy ratings during fear acquisition (Torrents-Rodas et al., 2014). Importantly, significant test-retest reliability was observed for maximum CS+ responding (SCRs: Fredrikson et al., 1993; Zeidan et al., 2012), CS- responding (SCRs: Fredrikson et al., 1993), as well as CS+/CS- discrimination during fear acquisition (SCRs, FPS and US expectancy: Krypotos et al., 2015, SCRs: Fredrikson et al., 1993), extinction recall and renewal (first two trials each in SCRs: Zeidan et al., 2012) as well as fear generalization (SCRs, FPS, US expectancy: Torrents-Rodas et al., 2014). Responding during extinction (last two trials) in turn did not display significant test-retest reliability (SCRs: Zeidan et al., 2012) possibly due to floor-level responding. Importantly, these findings are based on multiple fear conditioning sessions employing identical (Torrents-Rodas et al., 2014; Fredrikson et al., 1993; Zeidan et al., 2012) or different experimental stimuli (Torrents-Rodas et al., 2014) across sessions, with the former showing somewhat more compromised stability.

2.2. Data analysis considerations

Research on individual differences in fear conditioning has to date nearly exclusively relied on 'measures of central tendencies' in group-based analyses. Central tendency statistics assume that the mean is the best true population parameter and all variability represents random error. As outlined in detail in Section 1, a focus on average responding and treating variance around the mean as noise deprives us from insights into responding of individuals and subgroups. As such, a focus on mean responding may prevent us from the identification of clinically relevant subpopulations characterized by different response patterns.

Generally, research on individual difference factors requires targeted statistical approaches. In brief, these approaches can be based for

example on subgroups identified *a-priori* based on a known/observed variable (e.g., sex) or on a certain similarity concerning the pattern of individual response characteristics (e.g., response trajectories) in latent classes. To date, the field of individual difference research in fear conditioning reviewed here has nearly exclusively relied on the first scenario (for exceptions see Galatzer-Levy et al., 2017; Gazendam et al., 2014). As the field evolves (see also Section 5), other more advanced multivariate methods for the study of individual differences and in particular individual response trajectories (over time) can be expected to gain more and more importance and provide additional critical insights (see e.g., Galatzer-Levy et al., 2013).

In the following, we present a non-exhaustive set of data analysis considerations based on common issues in the current literature.

2.2.1. Direct statistical comparisons between groups and CSs

A direct statistical test for between-group differences (i.e., CS type x group interaction), for instance by employing mixed-models, is critically important for interpretation of the data. Within-group statistical tests (i.e., CS type main effect within one group) showing a significant effect in one but not in the other group cannot be taken to directly infer meaningful group differences (i.e., CS type x group interaction). However, within-group statistical tests should follow between-group statistical tests to identify the underlying response pattern driving the between-group differences as this may aid to pinpoint the underlying mechanisms. Besides, a separate follow-up analysis for between-group differences in responding towards CS + and CS- provides valuable information with respect to the mechanism (e.g., results are driven by inhibitory CS- or excitatory CS + related activation, given that no standardization has been employed before, which may mitigate potential inter-individual differences).

In addition to the frequentist approach and null-hypothesis significance testing as employed in most studies reviewed herein, the adoption of Bayesian statistics to the fear conditioning field has been discussed recently (Krypotos et al., 2016). In particular, as Bayesian hypothesis testing can identify if the obtained data support either the null or the alternative hypothesis, it can provide statistical evidence for equal responses towards the CS + and CS- or between groups, which is not possible when employing common null-hypothesis significance testing.

2.2.2. Potential mediating factors

Any inter-individual difference factor exerting an impact on fear conditioning processes might be mediated by its influence on a third variable. As a consequence, in addition to the analyses of main interest with respect to an inter-individual difference variable, analyses of group differences in or correlations with relevant third variables such as unconditioned responding, US aversiveness or CS-US contingency awareness need to be conducted and possibly controlled for. These analyses should always be provided in addition to results on conditioned responding.

2.2.3. Performance-based exclusion criteria

Pre-selection of or correction for individually-based (end-point) performance during fear acquisition or extinction or self-reported contingency awareness may induce a selection bias in favor of specific inter-individual difference factors. For instance, this might be the case when excluding all participants failing to show differential conditioning based on some (arbitrary) criterion in an arbitrary read-out measure following the rationale that extinction can only be studied in those individuals being successfully conditioned (for an in-depth discussion see Lonsdorf et al., 2017). Critically, end-point performance may in fact represent meaningful information on inter-individual differences rather than noise and this procedure is hence likely to significantly bias also extinction performance and/or generalizability of findings. Certainly, the employment of performance-based exclusion criteria might seem reasonable for specific research questions such as disentangling the

effects of fear learning and fear memory consolidation but performance-based exclusion or correction procedures may severely bias the results and unintendedly obscure true effects or bring about specific effects. Such procedures therefore require careful additional reporting of the absence of group differences between excluded and included participants and should absolutely be accompanied by the presentation of results in the full sample (i.e., reporting that results are not contingent on exclusion of particular subjects Simmons et al., 2011).

2.2.4. Dimensional vs. categorical analyses

In times of the Research Domain Criteria (RDoC; Insel, 2014; Anderson and Insel, 2006 Anderson and Insel, 2006), dimensional variables and a continuum from health to psychopathology are increasingly being employed to capture the full spectrum of variance as well as non-linear effects. Historically however, inter-individual difference research in fear conditioning has relied on samples where participants with current and/or lifetime mental disorders are excluded (see Fig. 2B). In addition, median split of 'convenience samples' has often been employed to turn a continuous variable into a categorical one. Median-split procedures have many disadvantages (for a dicsussion see e.g., Altman and Royston, 2006) for instance that every value above and below the median is considered equal − irrespective of its position in the continuum − which generally leads to a loss in resolution and hence power (McClelland and Irwin, 2003). Relatedly, recruitment of extreme groups may also lead to a loss in resolution, for instance in case of non-linear effects. Thus, a deeper understanding of the importance of any inter-individual difference factor is optimally achieved by a combination of dimensional and categorical approaches.

Supplementary Table 1 comprehensively lists whether a categorical or dimensional approach (when applicable) was employed across studies cited in this narrative review. We also refer to Fig. 3A for an exemplary illustration that mean trait anxiety scores of individuals assigned to as 'high' vs. 'low' trait anxious based on median-split or recruitment of extreme groups as well as the mean difference between both groups shows substantial variance (see Fig. 3B). For instance, the mean STAI trait score of individuals assigned to the 'high' group in one study may correspond more closely to the mean STAI trait score of individuals assigned to the 'low' STAI group in a second study (see Fig. 3A). It is hence conceivable that this impacts on the likelihood to detect the impact of inter-individual difference factors across studies and hence deserves more appreciation in future studies in particular when discussing non-convergent findings. Therefore, we recommend authors to always report the possible range of a given individual difference factor (e.g., STAI score) and the observed range in the test sample (i.e., the sample used for statistical calculations *after* exclusions) along with demographic characteristics of the sample.

2.3. Interim summary

2.3.1. Procedural and data analysis considerations

From the discussion on how procedural and data analysis specifics may impact on results of studies on inter-individual differences in fear conditioning, it should have become evident that methodological discussions and considerations are an important prerequisite for future advances in the field and a first step to oppose replication issues in the field. Researchers need to join forces and agree on *methodological* key points as well as the reporting of sample specifications, procedural and data analysis details in publications in the field − as recently done by joining forces across European labs (Lonsdorf et al., 2017). Factors listed in Supplementary Table 1 and 2 may serve as a preliminary guide and checklist on what factors should be included in scientific reports in order to allow for the identification of crucial differences in design and analyses that may lead to divergent findings and (seemingly) non-replications. Critically, large data sets are needed to investigate the impact of single and even more so for combinations of individual difference factors on fear conditioning processes (see also Fig. 4) by using
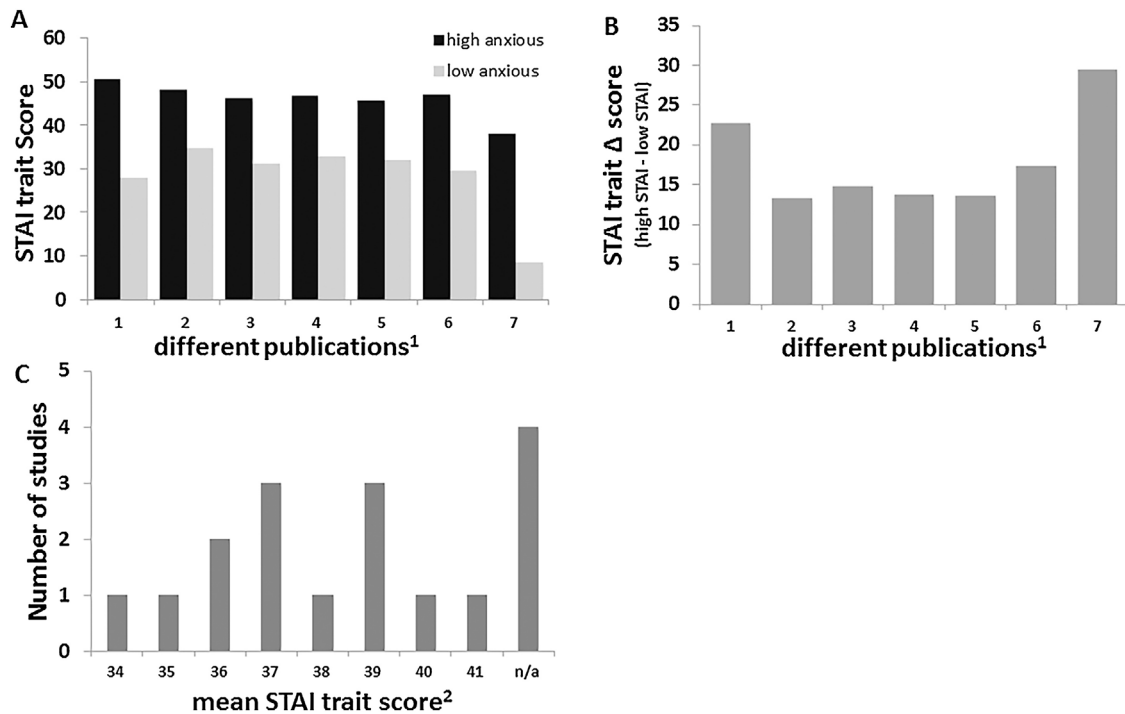
Fig. 3. Illustration of (A) mean STAI trait scores in groups labelled as 'high' and 'low' anxious across studies employing categorical analyses (see also Supplementary Table 1) (B) as well as mean difference in STAI scores between both groups across studies employing categorical analyses (i.e. median-split, recruitment of extreme groups) in studies investigating an association between STAI trait scores and fear conditioning. (C) Illustration of the mean STAI score (if available) across studies as derived from Supplementary Table 1.

[1]1: Glotzbach-Schoon et al. (2013b); 2: Barrett et al. (2006; Exp. 1); 3: Barrett et al. (2006, Exp. 2); 4: Gazendam et al. (2013); 5: Haddad et al. (2012); 6: Kindt and Soeter, 2014; 7: Torrents-Rodas et al. (2013). Note that the STAI version used by Torrents-Rodas and colleagues was the Spanish version with a possible range of STAI scores varying between 0 and 60 (and not 20–80 as in the other versions).

[2]only studies explicitly providing mean STAI trait scores in the full sample and listed under 'trait anxiety' in Supplementary Table 1 are considered. Studies providing STAI trait scores for different study groups, median or percentile scores are not represented in this figure.

Fig. 4. Schematic illustration between fear-related processes (i.e. fear acquisition, extinction, return of fear) and inter-individual difference factors. Fear-related processes are influenced by different mechanisms (illustrated within the light grey ring). Importantly, these mechanisms are not mutually exclusive and intertwined and are themselves subject to the influence of a variety of inter-individual difference factors (illustrated within the dark grey ring) as well as procedural factors (e.g., reinforcement rate, instructions, read-out measures, performance-based exclusion criteria;see chapter 2 and Lonsdorf et al., 2017 for a discussion). Hence, inter-individual difference factors impact on multiple processes involved in mechanisms underlying fear and anxiety that converge to a final common pathway of individual risk and resilience trajectories.

Note: While this figure exemplarily shows a normal distribution of risk and resilience, it has to be acknowledged that in clinical samples following trauma, most individuals in fact respond with resilience or recovery while only a small fraction develops chronic symptoms related to anxiety and PTSD (see e.g., Bonnano, 2004). Since we here however focus on experimental work in healthy individuals, a normal distribution is displayed in this figure (also according to a normal distribution of differential conditioned responding found in own unpublished observations). Nevertheless, please note that a normal distribution cannot be necessarily assumed to result from the processes and mechanisms illustrated in this figure and that also other distributions (e.g., skewed or multimodal distributions) might result from individual differences.
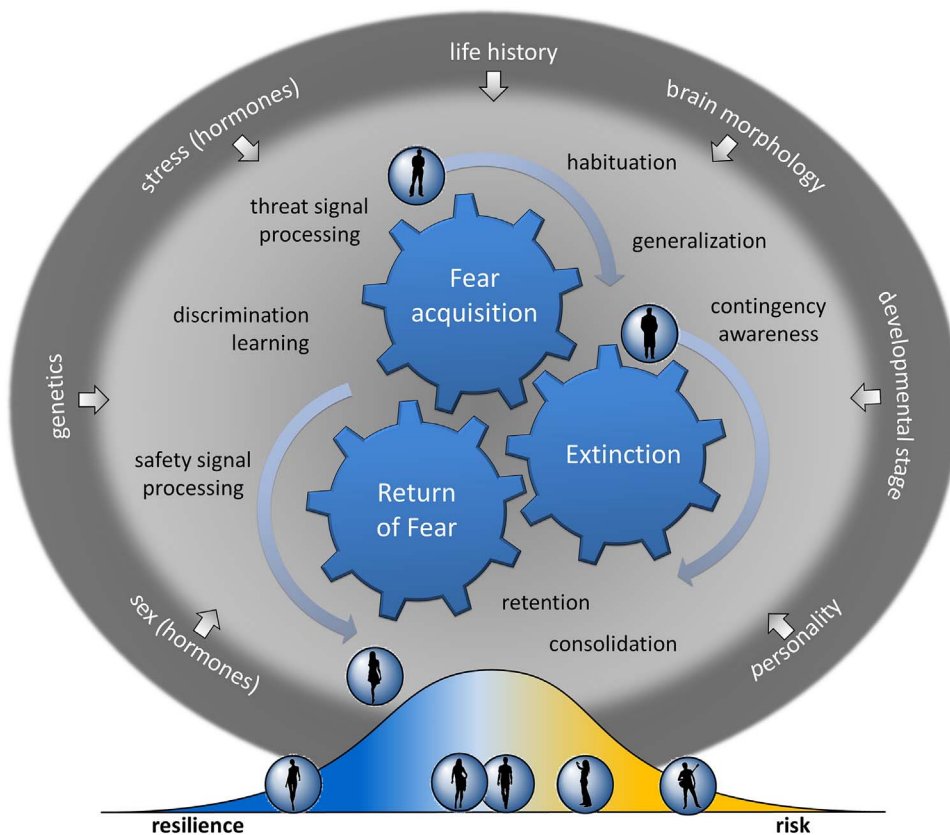
data analysis strategies suited for the investigation of individual differences. Thus, having recently compiled methodological key factors, the next step should be to investigate individual difference factors by using advanced and specifically tailored data analysis tools possibly in a joint effort across labs.

3. Biological and experiential variables

According to the classical nature-nurture debate in psychology, biological and experiential factors would represent influences conveyed by nature and nurture respectively. The past decades have however impressively demonstrated the inherently intertwined character of nature and nature. We accommodate this by grouping them together in the same subchapter. In the following we introduce relevant variables (i.e., age and development, sex and sex hormones, brain morphometry and volumetry, genetic polymorphisms, the stress hormone cortisol and life adversity, see 3.1–3.6) for the field of fear conditioning research and summarize findings based on experimental phases whenever feasible (i.e., based on the number of available publications) and develop suggestions for future studies from these summaries per inter-individual difference factor. We refer to Supplementary Tables 1 and 2 for specifics of the sample, outcome measures and procedures of the respective studies in full length and discuss specific methodological considerations relevant only to specific individual difference factors in these subchapters.

3.1. Age and development

Fear conditioning can be observed early in life which has been shown most impressively by the famous study of 'little Albert' nearly a century ago (Watson and Rayner, 1920) and demonstrated in children as young as three months by using SCRs (Ingram and Fitzgerald, 1974).

Importantly, pediatric anxiety often continues into adulthood (Bruce et al., 2005) and sex differences in anxiety (see also 3.2) do not manifest before the onset of puberty (Cover et al., 2014). Today, still little is known about developmental trajectories in fear conditioning processes and comparative studies, representing our focus, across the life span are largely lacking. A developmental perspective is however highly relevant, as brain regions supporting fear acquisition and extinction such as the amygdala, the hippocampus and the PFC undergo differential maturation processes with age (Jovanovic et al., 2013; Shaw et al., 2008; Shechner et al., 2014). Rodent work suggests that fear acquisition emerges early in life in line with early maturation of core regions involved in this process such as the amygdala. Relatedly, differential recruitment of early-maturing subcortical areas during fear acquisition has been reported in adolescents (aged 10–17) as compared to adults (aged 18–50; Lau et al., 2008).

In turn, extinction, in particular the ability for long-term retention of extinction, seems to emerge much later (Shechner et al., 2014; Kim and Richardson, 2010), which is in line with the later maturation of the PFC being considered to play a significant role in inhibition of fear (Lupien et al., 2009). Hence, a shift from amygdala-dependent to amygdala-independent extinction seems to be promoted by developmental processes (Shechner et al., 2014; Kim and Richardson, 2010). This work suggests that diverse mechanisms in fear learning and extinction, both neurally and pharmacologically, may act at different developmental stages, which would have direct and significant clinical implications (for a discussion see Kim and Richardson, 2010).

Of note, developmental studies in fear conditioning are however hampered by difficulties in assessing common measures (e.g. self-reports, fMRI) and important ethical considerations with respect to the use of aversive USs such as electrical stimulation in children. Thus, specific methods such as air-puff and light conditioning techniques (Shechner et al., 2014; Grillon et al., 1999; Grillon et al., 1998) or human faces paired with an aversive scream (Lau et al., 2008; Glenn et al., 2012a) have been explicitly developed for research in children

(for an overview on methodological details see Shechner et al., 2014, Pine et al., 2001). Yet, differences in US aversiveness across studies in children and adolescents poses interpretation difficulties across published studies (Glenn et al., 2012a; for discussion see Glenn et al., 2012b) as US potency has a strong impact on fear acquisition (see also 2). Furthermore, different cognitive abilities in different age groups may hamper interpretation of results (e.g., by resulting in differences in contingency awareness).

3.1.1. Fear acquisition and generalization

Comparable fear acquisition in SCRs (Lau et al., 2011; Pattwell et al., 2012; Schiele et al., 2016; Michalska et al., 2016) and retrospectively acquired fear ratings (Lau et al., 2008; Michalska et al., 2016; Den et al., 2015) as well as valence and arousal ratings (Schiele et al., 2016) have been observed in comparisons between different age groups of children (aged 5–10, 5–11 or 8–10), adolescents (aged 12–17) and adults (aged 18–51 and 18–28). Similarly, data from LaBar and colleagues (2004) suggest preserved differential SCR conditioning across the adult life span (18–80 years) despite a greater proportion of contingency awareness in young participants. Contingency awareness was better in older children (aged 9/10) than in younger children (aged 5–8; Michalska et al., 2016), pointing to the importance of taking differences in explicit memory into account when interpreting findings on developmental differences in fear conditioning research. Contingency awareness was however not assessed in a study in a large group of children (aged 3–8), which reported a linear increase in fear conditioning performance with age (Gao et al., 2010).

Despite these null findings, reduced discrimination between danger and safety cues in (online) fear ratings in adolescents (aged 10–17) compared to adults (aged 18–50) have been reported, which was accompanied by enhanced CS discrimination in early-maturing subcortical areas (amygdala, hippocampus Lau et al., 2011; Exp. 2). In addition, the activation of the dorsolateral prefrontal cortex correlated positively with fear ratings in adults and negatively in adolescents, suggesting that a possible shift in recruiting of late-maturing prefrontal areas might underlie differences in fear acquisition between adolescents and adults in this study (Lau et al., 2011; Exp. 2). Furthermore, reduced differential SCRs have also been reported for individuals older than 29 years as compared to those younger than 29 years (Rosenbaum et al., 2015). Finally, children below the age of 10 that were derived from a population with high trauma incidence showed poorer CS +/CS- discrimination (in FPS but not SCRs) as compared to children older than 10 years (Jovanovic et al., 2014).

Despite little converging and convincing evidence for a robust impact of biological age on fear acquisition, greater fear generalization (i.e. more shallow generalization gradients) during a subsequent generalization phase were observed in children (aged 8–10) compared to adults as indicated by explicit (verbal ratings) and autonomic (SCR) measures of arousal (Schiele et al., 2016) and in children aged 5–8 as compared to children aged 9–10 years in threat appraisal (fear ratings) and explicit memory (i.e., awareness), which was driven by less responding to stimuli similar to the CS + as compared to the CS + in older children as well as stronger responding to stimuli similar to the CS- (Michalska et al., 2016). These findings are in line with a previous preliminary report suggesting adult-like linear fear generalization pattern, as assessed by FPS, in older children (aged 11–13), whereas younger children displayed stronger startle responses to the CS- during the generalization test (Glenn et al., 2012b). Hence, there is some evidence suggesting a stronger tendency for generalization in young children below the age of 10.

3.1.2. Extinction and return of fear

No differences in extinction performance were observed in SCRs across the adult life span (groups aged 18–29, 51–64 and 66–80; Schiele et al., 2016)) or between individuals older vs. younger than 29 years (Rosenbaum et al., 2015). Adolescents in turn showed significantly

attenuated extinction learning after allowing for fear memory consolidation (i.e. delayed extinction) in SCRs as compared to children and trend-wise as compared to adults, a finding that was likewise observed in freezing behavior in mice (Pattwell et al., 2012). In particular, reduced extinction performance in adolescent samples, possibly resulting from altered synaptic plasticity in prefrontal areas implicated in fear inhibition (Pattwell et al., 2012), may have important clinical implications with respect to treatment efficacy and relapse risk. A single study investigating extinction recall and renewal (Rosenbaum et al., 2015) did not observe differences in differential SCRs between individuals older or younger than 29 years and no differences in extinction were observed between children older or younger than 10 years in SCRs or FPS (Jovanovic et al., 2014).

3.1.3. Summary and suggestion for future studies

Human work is in agreement with rodents work (for an overview see Shechner et al., 2014) in suggesting that normal 'developmental progress reduces generalization and sharpens discrimination' (cf. Schiele et al., 2016) and points to the direction that overgeneralization during childhood might represent a protective mechanism promoting cautious behavior that however may tip towards pathological anxiety. Still, there is limited converging evidence regarding the role of age on fear acquisition and extinction itself, even though attenuated extinction learning after fear memory consolidation in adolescents seems to be a promising finding that needs to be replicated and followed-up on. Furthermore, it should be considered mandatory to assess CS-US awareness in studies on developmental effects in fear conditioning research as robust differences in explicit memory for task contingencies have been reported which may bias interpretation of findings substantially if unaccounted for.

In addition, it becomes clear from Fig. 2D and Supplementary Table 1 that studies on inter-individual differences in fear conditioning have mainly relied on relatively young samples and future studies should explicitly pursue a developmental approach across the life-span. Currently, the interpretation of findings on the role of developmental factors in fear conditioning is limited as divergent associations may manifest themselves across differently operationalized age groups and age groups that do not differ strongly (i.e., children divided by age into different groups may only be a couple of days older or younger than children assigned to the other group). In particular as anxiety disorders typically first emerge during childhood or early adolescence (Beesdo et al., 2009; Costello et al., 2005; Pine et al., 1998), a developmental neuroscience perspective employing cross-sectional as well as longitudinal investigations holds promises to unravel early risk factors and developmental trajectories that may ultimately aid the development of targeted prevention and intervention programs. In particular the transition from childhood to (early) adolescence as well as other phases of transition (e.g. menopause, see 3.2) seems to represent particularly relevant time-windows that deserve intensified attention. In addition, given accumulating evidence for (neuro-) developmentally based differential efficacy of extinction learning, studies investigating experimental models of extinction recall and relapse (risk) are eagerly awaited to establish additional (long-term) consequences of possible extinction deficits.

3.2. Sex differences and sex hormones

Women are twice as likely to develop anxiety disorders than men (Jacobi et al., 2004; Kilpatrick et al., 2013) and affected women also display more severe symptoms than men (Holbrook et al., 2002; Seedat et al., 2005). Despite this sexual dimorphism, most experimental fear conditioning studies in rodents and humans have been conducted in males (for a reviews see Cover et al., 2014; Cahill, 2012; Lebron-Milad and Milad, 2012), while conclusions on studies in male participants are all too often generalized to females.

In addition to the biological sex, different levels of sex (or gonadal)

hormones occur over the course of the menstrual cycle in females, which has been shown to exert a pronounced impact on cognitive and affective processing (Sundström Poromaa and Gingnell, 2014; Toffoletto et al., 2014). The typical menstrual cycle lasts approximately 28 days with luteinizing hormone, follicle stimulating hormone and estradiol peaking around ovulation (day 14). Progesterone concentrations increase in the second half of the menstrual cycle (luteal phase) co-occurring with a second, albeit smaller peak in estradiol secretion. The onset of the menstrual bleeding marks the beginning of the next cycle with sex hormone levels dropping and reaching low levels during the so-called follicular phase. Moreover, the common intake of oral contraceptives (OCs; leading to low endogenous sex hormone concentrations; Lebron-Milad and Milad, 2012) or other hormonal preparations (hormonal controceptives, HCs) used for birth control in young women also critically influence cognitive and affective processes (Toffoletto et al., 2014; Lisofsky et al., 2016; Warren et al., 2014).

Sex differences in fear conditioning performance as well as an impact of sex on common read-out measures in fear conditioning such as SCRs has been recognized decades ago (Guimarães et al., 1991), but systematic investigations including sex hormones were only conducted during the recent past.

3.2.1. Fear acquisition and expression

During fear acquisition, extinction and recall, deficient CS-discrimination in SCRs, fear and US expectancy ratings was observed in healthy women compared to men (Lonsdorf et al., 2015). On the neural level however, higher differential neural activation (but not in SCRs) emerged in the amygdala and ACC in women compared to men (Lebron-Milad et al., 2012a). Results of an instructed fear paradigm revealed men to exert higher differential SCRs than women − albeit only in comparison to women taking OCs, not compared to free-cycling women tested in the luteal phase (Merz et al., 2013a). Differential amygdala activation was strongest in women in the luteal phase, which was both confirmed and extended to activation in the insula, cingulate cortex and hypothalamus (compared to men and OC women) in a recent study (Hwang et al., 2015). This implies that women might be especially sensitive to danger signals during this period. Likewise in patients with PTSD, women exhibited higher differential SCRs during fear acquisition than men (Inslicht et al., 2013). Other reports could not find any significant differences in SCRs in women with differing sex hormone levels (due to the menstrual cycle or OC intake) during fear acquisition (Graham and Milad, 2013; Li and Graham, 2016; Milad et al., 2010) or even the opposite pattern was observed with men exhibiting higher differential SCRs compared to free-cycling women (Milad et al., 2010). Using rectal distensions as US, OC women displayed higher CS +/CS- differentiation in the insula compared to men (Benson et al., 2014) suggesting that sex differences not only emerge in learning processes involving fear and exteroceptive US but also in fear-related learning of interoceptive US. Factors contributing to discrepancies in the mentioned studies on sex differences during fear acquisition need to be determined in the future, one of them might be the interaction of sex with stress hormones (see 3.5).

3.2.2. Extinction and return of fear

Rodent and human experiments revealed an impact of sex hormones on extinction (consolidation) processes. High levels of estrogens – as occurring naturally during the menstrual cycle or after pharmacological administration – have been shown to be favorable for extinction memory consolidation, as indicated by enhanced extinction recall in differential SCRs, FPS or freezing behavior. At the same time, low levels of estrogens (either due to the respective stage of the menstrual cycle or due to OC intake) have been shown to be disadvantageous for these processes (Graham and Milad, 2013; Milad et al., 2010; Chang et al., 2009; Glover et al., 2013; Milad et al., 2009b) and associated with impaired fear inhibition reflected in FPS (Glover et al., 2013). In rodents, administration of estrogens (immediately following extinction

training but not after four hours) abolished the extinction impairment in freezing behavior in female rats with low levels of estrogens pointing to a direct link between estrogens and extinction consolidation processes (Zeidan et al., 2011). Likewise, a median-split procedure in women revealed that those women with high estrogen levels exhibited higher vmPFC activation during extinction learning than women with low estrogen levels, which was also conformed in a correlation analysis of both measures (Zeidan et al., 2011).

Furthermore, women in the early follicular phase (with low sex hormone levels) receiving estradiol prior to extinction training exhibited less return of fear compared to placebo-treated women, also elegantly shown in different rodent experiments (Graham and Milad, 2013). Additionally, lower estradiol concentrations were associated with higher differential SCRs during extinction learning (and stronger intrusive memories of violent films implemented as US) in free-cycling women (Wegerer et al., 2014). Likewise, low levels of estrogens as evident in OC women as compared to women in the luteal phase and men have also been linked to deficient extinction learning in a neural circuit comprised of the amygdala, vmPFC, ACC and thalamus, while no effects were observed for SCRs (Merz et al., 2012a). An additional player in this neural circuit is the insula showing higher activation in women with high estradiol levels compared to men during late extinction and extinction recall (Hwang et al., 2015). Moreover, differential SCRs during extinction recall were reduced in women with high levels of estrogens accompanied by enhanced differential amygdala and vmPFC activation (Zeidan et al., 2011). Furthermore, OC women exerted decreased activation of the posterior cingulate cortex during extinction learning and increased differential responses in the hippocampus, thalamus and cerebellum after reinstatement compared to men in a conditioning model using rectal distensions as US (Benson et al., 2014). Women using HCs also displayed a dissociation between different outcome measures: While their SCRs towards the CS+ were higher during extinction recall compared to women with high estradiol levels, their US expectancy and ratings of CS valence were comparable (White and Graham, 2016).

Based on these findings, especially evidence for impaired fear extinction/inhibition, it has been proposed that low estradiol concentrations may represent a vulnerability factor for the development of PTSD and anxiety disorders (Lebron-Milad et al., 2012b). Importantly, these results have been recently extended from healthy to phobic women (Li and Graham, 2016): healthy as well as phobic women with low estradiol levels displayed increased SCRs during extinction recall compared to women with low estradiol levels.

3.2.3. Summary and suggestion for future studies

Circulating sex hormones and biological sex exert a critical impact on fear conditioning processes, which needs to be taken into account when both sexes are included in experimental samples. More precisely, pooling groups of women with and without HC usage into one group might cancel out potential effects of circulating (endogenous and exogenous) sex hormones (see 1.1). Methodologically, when including female participants, menstrual cycle phase and the use of HCs should at least be reported and at best be controlled for (for further methodological recommendations, please see Merz and Wolf, 2017), because both factors have a potent impact on different fear conditioning processes (Cover et al., 2014; Lebron-Milad and Milad, 2012; Lonsdorf et al., 2015; Milad et al., 2010; Merz et al., 2012a; Milad et al., 2006). Supplementary Table 1 gives an overview on how rarely menstrual cycle phase and use of OC or HC is conduced, hoping for future studies to take this into consideration.

Importantly, these findings hold promise to be translated to clinical settings: exposure therapy in women with anxiety or stressor-related disorders could be more effective at times of high sex hormone availability such as in the luteal phase (Glover et al., 2015). High sex hormone concentrations might promote extinction consolidation processes as delineated above and lead to less relapses in the long run.

Speculatively, the psychotherapist would simply need to time the exposure session to take place in the individual luteal phase of her/his female patient, a strategy which can be easily realized in everyday practice. For a more detailed discussion on this topic, we refer the interested reader to comprehensive reviews (Cover et al., 2014; Lebron-Milad and Milad, 2012; Stockhorst and Antov, 2015).

More clinical studies including sex (hormones) as moderating factors for therapy success are needed to study the translational potential for estradiol effects on fear conditioning processes. In addition, further sex hormones such as progesterone or testosterone and their concerted action should be investigated more intensively. A developmental perspective (see 3.1) should also include boys and girls as well as women in and after the menopause (in which sex hormone level dramatically drop) clearly calling for longitudinal studies.

3.3. Brain morphology and volumetry

Inter-individual differences in brain morphology, such as the volume of subcortical and thickness of cortical structures as well as structural integrity of connecting fiber tracts are primarily considered biological factors. Of note however, environmental influences on brain morphology have been established (e.g., (Dannlowski et al., 2011; Kuhn et al., 2016, for a review see Teicher et al., 2016) which once again demonstrates that nature and nurture are inherently intertwined. Notably, differences in brain morphology have been linked to variance in successful fear acquisition and extinction as well as extinction recall (as measured by SCRs).

3.3.1. Fear acquisition

More precisely, the strength of discrimination between signals of danger and safety (CS+ > CS-) in SCRs during cue conditioning has been positively related to volume of the right amygdala (during early acquisition in sample 1; during late acquisition in sample 2; Winkelmann et al., 2015) and the posterior insula (Hartley et al., 2011). This supports findings from an earlier study in a smaller, partly overlapping sample reporting a positive correlation with left amygdala volume (Cacciaglia et al., 2014).

In addition, SCRs to the CS+, but not the CS- or the differential score (CS+ > CS) were positively correlated with thickness of the dorsal anterior cingulate cortex in a small sample (Milad et al., 2007). Finally, individuals with larger hippocampi acquire SCR context conditioning significantly stronger than those will smaller hippocampi (Pohlack et al., 2012) as assessed by the second but not the first interval response (see Prokasy and Ebel, 1967), whereas amygdala volume did not relate to context conditioning (Pohlack et al., 2012).

3.3.2. Extinction and extinction recall

Stronger CS discrimination in SCRs during extinction was negatively correlated with the thickness of the (subgenual) anterior cingulate cortex (early immediate extinction:, Winkelmann et al., 2015) in two independent samples and the bilateral orbitofrontal cortex (OFC; early immediate extinction: Dannlowski et al., 2011) in one sample only. Thus, individuals with thicker prefrontal cortical areas seem to show faster extinction learning, which was mainly driven by reductions of SCRs towards the CS+ but not towards the CS-.

Furthermore, extinction recall, but not extinction learning, was positively correlated with thickness of the medial OFC when tested in the extinction context (Rauch et al., 2005) as well as the vmPFC when tested in both the acquisition (i.e., renewal) and extinction context (Milad et al., 2005). The latter finding was replicated using an exploratory statistical threshold (Hartley et al., 2011). However, the aforementioned study by Winkelmann and colleagues (2015) but also that of Hartley (2011) employed a partial reinforcement ratio (50% and 35–17% respectively), while Milad and colleagues (2005) and Rauch and colleagues (2005) used 100% reinforcement ratios most likely leading to non-comparable extinction learning curves, which may

explain these divergent findings.

3.3.3. Summary and suggestion for future studies

To date, a limited number of studies has linked brain morphology and volumetric estimates in areas known to be implicated in fear conditioning processes to autonomic measures of fear acquisition, extinction and extinction recall in however mostly small sample sizes (see Supplementary Table 1). Studies linking brain morphometry to return of fear are however largely lacking to date. It will be crucial for future studies to investigate if structural differences in volumetric estimates bias functional imaging data in particular as the vmPFC cluster linked to extinction learning covered the same area observed in fMRI studies (as discussed by Winkelmann et al., 2015). In addition, longitudinal studies in humans need to investigate causal questions, as rodent work has shown morphological changes, partly explained by increases in dendritic spine density, in the amygdala, insula and the auditory cortex following (auditory) fear conditioning (Keifer et al., 2015), which has not yet been addressed in humans.

In addition, first results regarding structural integrity of fiber tracts in (subthreshold) PTSD patients point to an involvement of fiber tracts connecting the vmPFC and limbic areas as well as the cingulate cortex with the hippocampus in extinction learning (Costanzo et al., 2016; Fani et al., 2015) and trait anxiety (Kim and Whalen, 2009). In the future, these findings need to be expanded to healthy individuals and acquisition as well as extinction recall (cf. Hermann et al., 2017) to gain a deeper understanding of the relevance of structural connectivity for fear conditioning processes (and their translation to patients with anxiety disorders; Ayling et al., 2012).

3.4. Genetic polymorphisms

Already in the 80ies and 90ies of the 20th century, epidemiological studies showed strong familial aggregation of anxiety disorders (for comprehensive reviews and meta-analysis see Hettema et al., 2001; Marks, 1986; Weissman, 1993). Subsequently, twin studies attributed the major source of familial risk (i.e. 30–40%) to additive genetic factors, which ultimately sparked the 'search for anxiety genes' (Hettema et al., 2001).

Ironically, despite of the once iconic status of Pavlovian conditioning as an epitome of learning and behaviorism, research has shown an impact on genetic factors on fear conditioning processes as well as their neurobiological underpinnings (reviewed in Lonsdorf and Baas, 2015; Lonsdorf and Kalisch, 2011; Sumner et al., 2015). The shifts in beliefs about whether human behavior is determined by genes (i.e. nature) or by environmental factors (i.e. nurture) is hence reflected in research on fear conditioning with an explosion of interest in 'gene x environment interactions' (GxE) in the last decade.

Despite the establishment of a heritable base already decades ago, it has not been before recently, that specific candidate polymorphisms have been identified that show associations with fear conditioning processes. By this means, genetic polymorphisms can serve as proxies for inter-individual differences in neurotransmitter levels or protein availability and may inform about the molecular mechanisms underlying fear conditioning processes. Moreover, research has shown that most complex human behavior as well as psychopathological conditions are most likely under polygenic influence with small effects of each individual genetic variant and additionally modulated by environmental experience (Munafò and Flint, 2014).

As this research field has been reviewed comprehensively and systematically elsewhere we refer the interested reader to these other sources for a summary and recommendations (Lonsdorf and Baas, 2015; Lonsdorf and Kalisch, 2011; Sumner et al., 2015) and limit ourselves to a brief summary of two of the most convergent findings.

Probably the most established association is between a genetic variant in the serotonin transporter gene promoter region, *5-HTTLPR*, and fear conditioning. This supports strong evidence implicating the

serotonin (5-HT) system in the acquisition and expression of fear (for a review see Bauer, 2015; Homberg, 2012). More precisely, drugs used to treat pathological anxiety and depression target the 5-HT system, such as selective serotonin reuptake inhibitors (SSRIs), which block the functioning of the serotonin transporter (5-HTT). A functional polymorphism in the *5-HTT* promoter region (*5-HTT* LPR) has been identified that comprises a 43 bp insertion/deletion polymorphism, resulting in a short (s) and a long (l) version differing in transcriptional efficacy (Heils et al., 1995).

The low-efficacy *5-HTT* LPR s-allele has consistently been associated with facilitated fear conditioning (i.e. enhanced CS + /CS- differentiation) in uninstructed (Pavlovian) designs (Garpenstrand et al., 2001; Wendt et al., 2015; Lonsdorf et al., 2009), instructed fear paradigms (Klumpers et al., 2015b; Klumpers et al., 2012 Klumpers et al., 2012) as well as observational fear learning (Crisan et al., 2009) as assessed by SCRs and FPS in humans. In addition, genotype-dependent activation of the dorsolateral prefrontal cortex during fear expression has been shown to mediate genotype-dependent inter-individual differences in physiological responding (SCRs and FPS; Klumpers et al., 2015). Furthermore, homozygous s-carriers displayed stronger differential (i.e. CS + > CS-) activation in a number of other areas of the neural network linked to fear processing such as the amygdala and/or the insula during fear acquisition (Hermann et al., 2012; Klucken et al., 2013; Klucken et al., 2014) as well as related experiments targeting the processing of uncertain threat (Drabant et al., 2012). These findings seem to be further moderated by life history (Hermann et al., 2012; Klucken et al., 2013) and might extend to the neural activation elicited by US. In addition, gene x gene interactions with other polymorphisms (Lonsdorf et al., 2009; Hermann et al., 2012; Agren et al., 2012; Glotzbach-Schoon et al., 2013a; Heitland et al., 2013) or mediation of effects by other *5-HTT* variants (Hartley et al., 2012) have been reported.

A second prominent example is a functional single nucleotide polymorphism in the pro-domain of the gene coding for brain derived neurotrophic factor (*BDNF* val66met). A vast preclinical literature implicates BDNF signaling in hippocampus- as well as amygdala-dependent learning in rodents (Ou and Gean, 2006; Rattiner et al., 2004; Rattiner et al., 2005; Tyler et al., 2002) such as fear conditioning and extinction (Andero and Ressler, 2012; Autry and Monteggia, 2012, ((Chen et al., 2004; Cunha et al., 2010; Martinowich et al., 2007; Soliman et al., 2010)))

In humans, a polymorphism in the *BDNF* gene coding for the replacement of valine by methionine at position 66 in the BDNF protein (*BDNF* val66met) leads to reduced activity-dependent secretion (Chen et al., 2004; Egan et al., 2003). The met-allele has been associated with attenuated fear acquisition and its retention as assessed by FPS as well as stronger CS-discrimination in the amygdala and the subgenual anterior cingulate cortex in fMRI (Hajcak et al., 2009; Lonsdorf et al., 2010; Lonsdorf et al., 2014a; but see Torrents-Rodas et al., 2012). Furthermore, the met-allele has been linked to stronger fear generalization (Mühlberger et al., 2013) and to deficits in extinction learning in rodents and humans (Chen et al., 2004) even though the human results of this study are ambiguous (for a discussion see Lonsdorf and Kalisch, 2011) and have not been replicated by others (Lonsdorf et al., 2010; Lonsdorf et al., 2014a; Torrents-Rodas et al., 2012). Despite, the *BDNF* val66met polymorphism has been linked to response to CBT, which heavily relies on the principles of extinction learning (Felmingham et al., 2013; Fitzgerald et al., 2014; Fullana et al., 2012).

3.4.1. Summary and suggestion for future studies

Studying the genetic basis of experimental fear learning, extinction and return of fear has potential to further our mechanistic neurobiological understanding of risk and resilience trajectories to stress- and anxiety-related pathology. Whereas early work in humans followed hypothesis-driven candidate gene approaches, recent methodological advances such as the feasibility of large scale sequencing- and array-based techniques (realized in genome-wide association studies, GWAS),

as well as new statistical developments and machine learning algorithms hold promise to lift the field further. The interplay between these methodological advances and mega-analysis of 'big data' originating from translational collaborative research centers (Reif et al., 2014; Kuhn et al., 2016c; Straube et al., 2014) or consortia (e.g. Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) will be powerful in unraveling the neurobiology of fear acquisition, extinction and return of fear.

3.5. The stress hormone cortisol

Stress and stress hormones strongly influence cognitive and emotional processing and lead to lively remembrance of emotionally arousing events (Wolf, 2008). Neurobiologically, an (anticipated) environmental threat activates the stress response by stimulating the sympathetic nervous system (SNS) as well as the hypothalamic-pituitary-adrenocortical (HPA) axis. On the one hand, activation of the SNS leads to the rapid release of adrenaline and noradrenaline from the adrenal medulla and the sympathetic nerves causing the typical stress symptoms such as accelerated heart rate or higher blood pressure. On the other hand, activation of the HPA axis stimulates the release of corticotropin-releasing hormone from the hypothalamus, which in turn leads to the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. In the end, ACTH triggers the adrenal cortex to release glucocorticoids such as cortisol, the major stress hormone in humans, into the bloodstream. In contrast to the rapidly initiated release of adrenaline and noradrenaline, the cortisol peak occurs not until 20–30 min after onset of the stressor (Dickerson and Kemeny, 2004).

Importantly, cortisol can easily pass the blood-brain barrier and exert its effects on different brain structures involved in learning and memory processes (for reviews: Joëls and Baram, 2009; Schwabe et al., 2012). In declarative memory, on the one hand, rapid non-genomic cortisol effects (in interaction with catecholamines) in the basolateral amygdala are supposed to facilitate encoding and early consolidation of ongoing information processing, but to inhibit competing cognitive operations such as memory retrieval. Within this 'memory formation mode' the amygdala also targets the hippocampus or prefrontal cortex to particularly modulate processing of emotional information. On the other hand, genomic cortisol actions seem to promote recently learned information to be stored into long-term memory ('memory storage mode'), whereas unrelated ongoing information processing is suppressed (Schwabe et al., 2012). Since the amygdala, hippocampus and prefrontal cortex are also critically involved in fear conditioning processes, it is not surprising that stress effects have been found to substantially modulate them (Rodrigues et al., 2009) with assumed parallel mechanisms as observed in declarative memory (de Quervain et al., 2017).

Here, we restrict ourselves to studies investigating the impact of cortisol on fear conditioning processes, since the available evidence on cortisol effects in humans is much higher compared to other stress mediators. We refer the interested reader to a recent review for further information about other relevant stress mediators such as catecholamines (Stockhorst and Antov, 2015).

3.5.1. Fear acquisition

The stress-induced changes in systolic and diastolic blood pressure have been positively related to differential SCRs during fear acquisition in men, when exposure to stress occurred close (10 min) to fear acquisition training (Antov et al., 2013). When the gap between stress and fear acquisition is extended long enough for cortisol reaching its peak concentrations (approximately 40 min after stress onset in this case), a negative relationship between stress-induced changes in cortisol concentrations and differential SCRs was observed during fear acquisition and extinction in men (Antov et al., 2013). However, one hour after stress induction (Jackson et al., 2006), higher differential SCRs were found in the stress compared to the control group during fear

acquisition and late (immediate) extinction in men (also seen in correlational analyses), which could be traced back to heightened reactivity towards the CS +. In women, stress led to decreased differential SCRs only during early (immediate) extinction in this study. Indeed, further hints exist for sex differences, for example, elevated cortisol concentrations after fear acquisition have been shown to facilitate consolidation of fear acquisition memories as evident in differential neural activation and SCRs in men (Merz et al., 2014a; Zorawski et al., 2006; Zorawski et al., 2005), but not in women (Zorawski et al., 2006; Zorawski et al., 2005). Moreover, stress induction taking place 45 min prior to fear acquisition and immediate extinction did not influence both learning phases in three groups differing in sex hormone status (men vs. women in the early follicular phase vs. women in the midcycle phase; Antov and Stockhorst, 2014).

Pharmacological administration of cortisol before fear acquisition also demonstrated sex-dependent effects: cortisol attenuated differential activation of the fear network in men and women tested in the follicular and luteal phase of their menstrual cycle, but heightened differential activation in women taking OCs (Merz et al., 2010; Merz et al., 2012b; Stark et al., 2006; Tabbert et al., 2010). Interestingly, the same result pattern of differential brain activation was found after exposure to a psychosocial laboratory stressor: whereas stress reduced differential CRs in men, it increased them in OC women, e.g. in the amygdala (Merz et al., 2013b). Furthermore, cortisol application attenuated fear contextualization and intensified fear generalization in FPS in OC women, whereas the opposite pattern was found in men (van Ast et al., 2012). Differential SCRs were reduced after cortisol administration in this study, but only in men. Taken together, interactive effects of stress and sex hormones on fear acquisition and generalization seem to reliably occur and need to be considered in future studies concerning this topic. Another topic would encompass the precise characterization of rapid non-genomic in contrast to slow genomic cortisol effects as shown in men (Cornelisse et al., 2014): Cortisol administration 240 min prior to fear acquisition (tackling slow genomic cortisol effects) facilitated consolidation of trace fear conditioning as evidenced 24 h later in higher differential FPS during early extinction. This effect was limited to trace conditioning, FPS as outcome measure and slow genomic cortisol effects; no effects could be found for delay conditioning, SCRs, US expectancy ratings or rapid non-genomic effects, for which cortisol application was realized 60 min before fear acquisition.

3.5.2. Fear extinction and extinction recall

Our understanding of the effects of cortisol on fear extinction and extinction recall is less advanced compared to the results obtained for fear acquisition. As mentioned above, when stress was induced approximately 45 min before acquisition training and immediate extinction, a negative relationship between cortisol increases and differential SCRs occurred in men (Antov et al., 2013). But stress induction 60 min before fear acquisition and immediate extinction revealed higher differential SCRs during late extinction in men, but lower differential SCRs during early extinction in women (Jackson et al., 2006). More specifically, a study including OC women only revealed pre-acquisition cortisol administration to attenuate activation in the fear network surrounding the amygdala during immediate extinction (Tabbert et al., 2010). However, pre-acquisition stress induction did not exert an impact on immediate extinction in men, women in the follicular phase and women in the midcycle phase of their respective menstrual cycle (Antov and Stockhorst, 2014). But 24 h later, extinction recall in SCRs was reduced in women in the early follicular phase compared to men. Separating stress effects on extinction learning from acquisition, pre-extinction stress was found to reduce differential US expectancy during fear recall (observed during early extinction one day after fear acquisition and early fear recall on a third day) in men but not in OC women (Bentz et al., 2013). Thus, sex hormones interact with stress hormones in mediating effects on extinction learning. In particular low levels of female sex hormones (either from low levels during the follicular phase

or from OC intake) in combination with cortisol increases seemingly leads to a resistance to extinction (cf. Maeng and Milad, 2015).

Since exposure therapy taps into the mechanisms of extinction learning, patient studies can shed additional light on applied aspects of stress-induced modifications of learning and memory processes. Indeed, patients with spider, social or height phobia (de Quervain et al., 2011; Soravia et al., 2006; Soravia et al., 2014) reported less fear during exposure as well as at follow-up sessions when cortisol was given before exposure. According to the literature on declarative memory, these translational findings can be explained as follows (de Quervain et al., 2017; Bentz et al., 2010; de Quervain and Margraf, 2008): Cortisol attenuates fear recall in patients encountering their feared stimulus during exposure therapy. At the same time, cortisol facilitates consolidation of the corrected fear memory, complementing the beneficial effect of cortisol administration. Furthermore, pharmacologically enhanced noradrenergic activity before exposure therapy also reduced fear at follow-up in patients with claustrophobia (Powers et al., 2009) or social phobia (Smits et al., 2014) but not in patients with fear of flying (Meyerbroeker et al., 2012).

Due to the pronounced circadian rhythm of cortisol (peak concentrations in the morning decreasing over the day to reach a minimum during midnight), also effects of daytime seem to be relevant for fear conditioning processes and exposure therapy. Indeed, exposure therapy in the morning (high cortisol concentrations) was related to a more pronounced attenuation of phobic fear during a behavioral avoidance test in patients with spider phobia compared to exposure sessions in the afternoon (low cortisol concentrations; Lass-Hennemann and Michael, 2014). In accordance, an association between high cortisol concentrations after awakening (the so-called cortisol awakening response) and improved exposure therapy outcome was found in patients with panic disorder and agoraphobia (Meuret et al., 2015).

Back to healthy individuals, exposure to stress after fear acquisition and immediately before extinction training improved extinction learning and recall in men (Antov et al., 2015). But stress induction after extinction training (to investigate the effects of stress hormones on extinction consolidation processes) led to an increased return of fear evident in SCRs in the acquisition (i.e. renewal) but not in the extinction context (Hamacher-Dang et al., 2015). Hypothetically, stress eased the integration of contextual information regarding extinction training into long-term memory or enhanced contextual boundaries of extinction memories. Moreover, stress application before fear recall reduced differential SCRs in the acquisition context (i.e. renewal) and also generally lowered SCRs in the extinction context (Merz et al., 2014b), which is in line with findings of a stress-induced impairment of emotional memory recall and results of the aforementioned clinical studies (de Quervain et al., 2011; Soravia et al., 2006; Soravia et al., 2014; Lass-Hennemann and Michael, 2014; but see Raio et al., 2014).

3.5.3. Summary and suggestion for future studies

The impact of the stress hormone cortisol on fear conditioning processes varies as a function of timing relative to the respective experimental phase and as a function of sex (hormone status). On the one hand, high cortisol concentrations inhibit the fear network seen during fear acquisition in men and free-cycling women, but leads to increased differential brain activation in OC women. On the other hand, high cortisol concentrations before (delayed) fear extinction or recall appear to reduce (phobic) fear responses resulting in beneficial effects in terms of inhibited fear recall. From a clinical perspective, these stress-induced modified fear conditioning processes might translate into crucial vulnerability factors for the development of an anxiety disorder or PTSD, but also to possible treatment options (cf. Merz et al., 2016). The interested reader is referred to other sources for a more detailed discussion of the underlying mechanisms (Merz and Wolf, 2017; Stockhorst and Antov, 2015).

Taken together, the crucial timing aspect of cortisol increases relative to the experimental phase is largely known from the effects of

stress hormones on declarative memory (Schwabe et al., 2012). Mechanistically, the relevance of the differential occupation of the two cortisol receptors as well as in interaction with the SNS remains to be shown in future work, especially concerning the translation to psychopathological conditions (Finsterwald and Alberini, 2014).

3.6. Life events and previous encounters

Life events are well established risk factors for the development and relapse of affective psychopathology (Beesdo et al., 2010; Moreno-Peral et al., 2014) and hence represent an inter-individual difference factor of strong interest for experimental models thereof. Surprisingly, little research has however been performed in this field to date in humans (for a review on primary rodent work see Leuner and Shors, 2013).

It is established that previous experiences have the power to affect conditionability (Mineka and Sutton, 2006) as impressively demonstrated by pre-exposure phenomena such as latent inhibition, that is, experiences with a stimulus (the CS) prior to conditioning attenuates conditioning with respect to a new CS. This phenomenon has been shown in observational conditioning in primates (Mineka and Cook, 1986) and has been translated to the acquisition of clinical phobias, where non-traumatic experiences with the trauma-inducing event served as a protective (i.e. 'immunization') factor for the development of pathology (Kent, 1997). In addition, the observation of a non-fearful model has been shown to cause immunization to fear acquisition in primates (Mineka and Cook, 1986) and humans (Golkar and Olsson, 2016). An additional example of (updated) previous experiences affecting subsequent CRs is the phenomenon of UCS revaluation that should only be mentioned for completeness here (Davey, 1989; Hosoba et al., 2001; Schultz et al., 2013; White and Davey, 1989).

In addition, exposure to life events has recently been shown to impact on fear conditioning processes in healthy children, adolescents and adults (i.e. without having developed PTSD after exposure to adversity; McLaughlin et al., 2015). A group of children and adolescents (6–18 years old) without maltreatment exhibited normal differential acquisition of CRs as assessed by SCRs. Maltreated children, as assessed by the Childhood Trauma Questionnaire (CTQ), however showed delayed acquisition of differential SCRs as manifested in differential responses occurring only during late acquisition. Furthermore, maltreated children exhibited blunted SCRs responses specifically to the CS+, whereas verbal ratings of fear did not differ between groups (McLaughlin et al., 2015).

In young adults (mean age: 25 years), however, no effect of childhood maltreatment (as assessed by the CTQ as well as a life calendar) or recent life adversity (as assessed by the list of threatening events; Brugha et al., 1985) was observed during the acquisition or (delayed) extinction learning in SCRs, ratings of fear or neural activation patterns (Scharfenort et al., 2016). After allowing for a 24 h consolidation period following fear acquisition participants returned to the laboratory. During this fear recall (i.e., first trials of extinction) and subsequent return of fear test following reinstatement (as an experimental model of adversity induced relapse of fear) however, adults not exposed to recent adversity showed strong reinstatement of differential SCR responding, while adults exposed to recent life adversity failed to exhibit differential responding (i.e. they displayed generalized reinstatement). These findings seem to be primarily driven by blunted CS+ responding and align with results reported above in children. Importantly, group differences in differential SCRs during both fear recall and return of fear were on a neural level reflected in group differences in hippocampal activation (Scharfenort et al., 2016), a core area implicated in stress (Kim et al., 2015), reinstatement of fear in rodents and humans (Haaker et al., 2014; Lonsdorf et al., 2014b) and in particular CS-discrimination during return of fear (Scharfenort and Lonsdorf, 2016). Of note, in both studies, similar results were obtained for dimensional (i.e. cumulative) scores of exposure to life adversity on both the autonomic (SCRs) and neural level and categorical measure (exposed vs. unexposed). On a

dimensional level, also childhood maltreatment was negatively associated with CS-discrimination during return of fear testing which again was mirrored in group differences in hippocampal activation (Scharfenort et al., 2016), results not manifesting when employing categorical grouping (see 2.2. for a discussion on disadvantages of making dimensional variables categorical). In addition, it has recently been shown that adults (mean age: 30 years) with and without exposure to childhood adversity (as assessed by the CTQ) differ in intra-and extra-amyloid causal connectivity during processing of an aversive event (i.e. US; Grant et al., 2015).

3.6.1. Summary and suggestion for future studies

Life experiences are capable of shaping the structure (Kuhn et al., 2016a; Paquola et al., 2016; Teicher et al., 2012) and functionality (Teicher et al., 2012; Scharfenort et al., 2016) of neural circuits underlying fear acquisition, extinction and return of fear processes. Hence, understanding the mechanisms by which life adversity acts on these processes has profound implications for the understanding of and possibly the prevention of pathological anxiety in the aftermath of exposure to life adversity.

Research on this important topic is however still in its infancy. To date only two studies exploring the role of exposure to life adversity on experimental fear conditioning, extinction and return of fear have been published. Thereby, maltreatment during childhood was linked to reduced CS discrimination during fear acquisition in children and exposure to recent adversity during early adulthood was also linked to reduced CS discrimination during fear recall and return of fear. As exposure to childhood maltreatment during childhood can in principle be classified as exposure to recent adversity, future studies need to replicate and extend these important leads. Future studies need to address this topic by employing prospective and longitudinal studies (i.e. developmental trajectories, cf. 3.1). Furthermore, there is a need for a more fine-grained investigation of the quality and quantity of life adversity as well as its developmental timing.

3.7. Interim summary: biological and experiential variables

In sum, there is evidence for the impact of serval biological and experiential inter-individual difference factors in the field of fear conditioning, an important area of experimental psychopathology. Despite a number of studies in total, evidence is limited for every single inter-individual difference factor, which is reflective of a field that is still in its infancy as interest in variance beyond the average is a fairly recent development. Future research needs to target the exact mechanisms underlying the reported associations and provide systematic investigations. To date large-scale studies taking into account multiple of these factors as well as their interplay and employing appropriate statistical tools and mediation analyses are largely lacking. Future work should assess and report the frequency of these factors in their study sample whenever feasible. This can be easily implemented for age, sex, HC/OC use, life history but can be quite challenging for other factors such as genetics, hormone levels and brain morphology.

4. Temperamental variables and cognitive biases

Historically, several theories on personality (Eysenck, 1967; Grey, 1982; Spence and Spence, 1966) make predictions about fear conditioning (for a review and empirical test see Revelle and Zinbarg, 1989) based on the idea that particular personality traits may predispose some individuals to enhanced fear conditionability (i.e. higher CS +/CS- discrimination). For example, Eysenck postulated that extraverted individuals less readily acquire CRs as a consequence of their lower arousal levels − in particular under certain experimental conditions such as partial reinforcement, differential conditioning, weak USs and short CS-US intervals (Eysenck, 1967).

According to our focus on the recent literature, we refrain from an in-depth discussion of reports on less commonly studied, albeit potentially interesting additional measures (see Supplementary Tables for details however) such as trait worrying (Joos et al., 2012; Nelson and Shankman, 2011; Otto et al., 2007), the depression anxiety stress scale (DASS) (linked to discriminatory fear learning and avoidance: Arnaudova et al., 2013), the stress reaction scale of the Multi-dimensional Personality Questionnaire (MPQ) (positive association with discrimination learning: Gazendam et al., 2014), Behavioral Inhibition Scales (BIS; Staples-Bradley et al., 2016), the Anxiety Sensitivity Index (linked to orienting responses but not conditioning: Otto et al., 2007) or extraversion (mixed associations with fear conditioniong: Otto et al., 2007; Fredrikson and Georgiades, 1992; Pineles et al., 2009).

4.1. State and trait anxiety

Anxiety is commonly separated into a state and a trait dimension that are usually assessed by means of the State and Trait Anxiety Inventory (STAI; Spielberger et al., 1983), which is considered a measure of negative affect in general rather than a pure measure of anxiety (for a discussion see Bados et al., 2010). State anxiety refers to how anxious the individual is *at the moment* (intra-individual differences), whereas trait anxiety refers to how anxious the individual is *in general* (inter-individual differences). Trait anxiety, as assessed by the STAI, is by far the most commonly investigated individual difference factor in the field of fear conditioning research. Investigating performance during different experimental fear conditioning processes in individuals differing in anxiety levels has the potential to elucidate the deviant mechanisms underlying pathological anxiety. Findings will be reviewed in the following and supplemented by a short paragraph on experimental work targeting state rather than trait anxiety in fear conditioning.

4.1.1. Fear acquisition, expression and generalization

Higher trait anxiety scores were linked to stronger differential conditioning (i.e. CS + > CS- or $CS_{predictable} >$ CS_{safe}) in SCRs (Indovina et al., 2011;see Sjouwerman et al., unpublished for a study showing a negative correlation in a large sample of 288 individuals), FPS (Gazendam et al., 2013) and distress ratings (Gazendam et al., 2013). Differences in CS discrimination were driven by stronger CS+ responses linked to high trait anxiety (Indovina et al., 2011; Sjouwerman et al., unpublished), while other studies have linked stronger fear responses to safety signals (i.e., CS-) but not signals of danger (i.e., CS+) to high trait anxiety by using FPS (Gazendam et al., 2013), distress ratings (Gazendam et al., 2013), but not SCRs (Gazendam et al., 2013) or US expectancy (Gazendam et al., 2013; Kindt and Soeter, 2014). It appears that studies linking trait anxiety-related CS-discrimination differences in SCRs to increased *CS+ responses* relied on experimental designs employing a 100% reinforcement rate − and hence inducing a rather unambiguous (i.e., strong) experimental situation (see Ozomaro et al., 2013). But studies linking trait anxiety to *inhibitory processing* of cues and context seem to be characterized by more ambiguous experimental situations through the employment of lower reinforcement rates (50%–87.5%: Haddad et al., 2012; Gazendam et al., 2013; Kindt and Soeter, 2014; Haaker et al., 2015). A systematic investigation of this potential experimental boundary condition is however not possible since not all studies provide

information on which submechanism drives individual differences in CS discrimination calling for greater attention to this idea in future studies.

Critically, some studies reported an impact of trait anxiety on one read-out measure but not on other read-out measures. For instance, Gazendam et al. (2013) as well as Haddad et al. (2012) did not report an impact on SCRs responding but observe effects on other read-out measures (see above), whereas Sjouwerman et al. (unpublished) observed an effect for SCRs but not fear ratings and Kindt and Soeter, 2014 reported effects for US expectancy but not FPS. To date it remains unclear whether some measures might be particularly sensitive to capture inter-individual differences in fear conditioning related to trait anxiety. Future studies should employ multimodal approaches and pay particular attention to this issue.

Of note, the majority of studies however has not observed an effect of trait anxiety on differential fear conditioning in any of the included behavioral (i.e. reaction times), physiological (i.e., SCR, FPS) and subjective (i.e. ratings of fear, valence, distress and US expectancy) measures of conditioned responding (Joos et al., 2012; Arnaudova et al., 2013; Chin et al., 2016; Martínez et al., 2012; Morriss et al., 2016a; Sehlmeyer et al., 2011; Torrents-Rodas et al., 2013).

Surprisingly, little research has investigated the relationship between fear acquisition or expression and trait or state anxiety on the neural level. In one single study, employing a mixed context-cue design, Indovina et al. (2011) demonstrated a positive correlation between trait anxiety and amygdala activation during fear expression (i.e. second fear acquisition phase occurring 48 h after fear acquisition) to the danger cue (CS +) in a threatening as compared to a safe context a finding supported by Sjouwerman et al. (unpublished) who simultaneously acquired SCRs and neural activation in the same learning session. Note however that correlation between SCRs and trait anxiety showed opposite results across both studies. In addition, differential amygdala activation ($CS_{predictable} > CS_{safe}$) during fear expression correlated positively with differential SCRs acquired during fear acquisition 48 h earlier. Others however did not observe associations between trait anxiety and neural activation or autonomic responding in cue (Sehlmeyer et al., 2011) or context conditioning with low (25/33%) reinforcement ratios. Recently, Sjouwerman et al. (under review) confirmed a positive correlation between trait anxiety and amygdala as well as thalamic and putamen activation during fear acquisition as well as a positive correlation between differential SCRs and differential amygdala activation in a study with a large sample size.

Importantly, a positive correlation between differential SCRs and differential amygdala activation during fear acquisition has been reported (MacNamara et al., 2015; Furmark et al., 1997) irrespective of trait anxiety. Indeed, Sjouwerman et al. (under review) provide evidence for a partial mediation of the impact of trait anxiety on differential SCRs via differential amygdala activation.

In sum, the picture emerging for an association between trait anxiety and fear conditioning is not crystal clear. However, it can be speculated that the large number of null findings may be related to procedural factors promoting unambiguous experimental situations (as discussed in 2.1) such as high reinforcement rate − however empirical evidence is required. In this respect, it is noteworthy that many of the studies on trait anxiety employed high reinforcement rates (e.g., 100% see Fig. 2A). However, a study employing a large sample size has recently demonstrated an impact of trait anxiety on neural and autonomic responding during fear acquisition with a 100% reinforcement rate (Sjouwerman et al. under review). Fear generalization paradigms however represent particularly ambiguous experimental situations. Again however, trait anxiety did not show an association with fear generalization as assessed by FPS, SCR and risk ratings (Torrents-Rodas et al., 2013) or avoidance (Lommen et al., 2010) and only limited evidence for stronger generalization (i.e., reduced discrimination) in FPS but not SCRs or fear ratings in high anxious individuals (Haddad et al., 2012).

4.1.2. Context-dependent learning and CS-US awareness

To date, research on the relationship between trait anxiety and fear conditioning processes has been primarily limited to cue conditioning and conditioned cue inhibition paradigms. Studies investigating the modulatory role of the context are sparse to date (Haaker et al., 2015, such as Baas, 2013; Bass and Heitland, 2015; Glotzbach-Schoon et al., 2013b). These studies revealed faster acquisition but comparable extinction of context conditioning in high trait anxious individuals as assessed by FPS but not for skin conductance level or affective/US expectancy ratings (Glotzbach-Schoon et al., 2013b). These data are well in line with rodent work showing that impaired cue discrimination co-occurs with enhanced freezing in threatening contexts (Duvarci et al., 2009). Furthermore, deficits in safety signal processing was positively correlated with trait anxiety − irrespective of safety being conveyed by a cue or context (Haaker et al., 2015).

Consideration of contextual factors is of critical importance, since trait anxiety has been linked to a tendency for context conditioning (Grillon, 2002b) and since fear extinction has been shown to be inherently bound to the context in which (extinction) learning takes place (Bouton and King, 1983; Maren et al., 2013).

Relatedly, previous work demonstrated that highly anxious participants seem to have difficulties in recognizing CS-US contingencies (Grillon, 2002b; Baas et al., 2008; Chan and Lovibond, 1996; but see Baas, 2013) and may hence show generalized fear responses (Chan and Lovibond, 1996). Deficits in contingency awareness again are associated with increased subjective and physiological signs of anxiety (Baas et al., 2008) and avoidance (Grillon, 2002b). To this end, it has been suggested that fear inhibition might depend on and be consequential to reduced US expectancy (Kindt and Soeter, 2014). Indeed, individuals scoring high on trait anxiety have difficulties in learning (action-outcome) contingencies changing over time in aversive environments as assessed by pupil dilation and modelling of learning rates (Browning et al., 2015). Others have however linked state but not trait anxiety to CS-US awareness (Prenoveau et al., 2011). This is of clinical significance, as associative learning deficits deprive individuals of situational warning signs (e.g. for a panic attack) and thus render the situation (e.g. the panic attack) unpredictable. Unpredictability then might further promote contextual anxiety, which again promotes CS generalization (which may however also be related to unpredictability directly). Correspondingly, participants that failed to acquire cue-related CS-US contingencies displayed stronger contextual fear (as assessed by FPS but not ratings). After information about contingencies were provided, trait anxiety correlated positively with contextual fear in previously unaware participants (Baas and Heitland, 2015). Furthermore, individuals with high trait anxiety showed a reduced ability to regulate (i.e. reduce) contextual fear after the introduction of a predictive cue (Baas, 2013) as assessed by FPS and fearfulness ratings.

In sum, high levels of trait anxiety have been linked to deficits in safety signal processing and difficulties in learning the predictive value of danger signals (CS-US contingency awareness) which again results in pronounced contextual anxiety.

4.1.3. Extinction and return of fear

Slower decreases in responding to both CS+ and CS- in FPS as well as generally higher distress to both CSs was observed in high trait anxious individuals during delayed extinction (Gazendam et al., 2013) despite of no differences in US expectancy or SCRs (Gazendam et al., 2013). Others did not observe an association between differential SCRs and trait anxiety, while differential amygdala activation during early (immediate) extinction were shown to be positively associated (Sehlmeyer et al., 2011). A positive association between differential amygdala activation and trait anxiety during immediate extinction was confirmed in a second study (Barrett and Armony, 2009a), whereas a negative association was reported for delayed extinction (Sjouwerman et al. unpublished).

Relatedly, during return of fear, mostly operationalized as

reinstatement, reduced differentiability of CS responses in SCRs and FPS has been related to trait anxiety in several preliminary reports (Kindt and Soeter, 2013; Kindt et al., 2009; Soeter and Kindt, 2010) but not others in either SCRs, FPS or ratings of distress and US expectancy (Gazendam et al., 2013; Martínez et al., 2012). Furthermore, a study on extinction recall and renewal did not observe any effects as assessed by SCRs (Martínez et al., 2012).

On the neural level, trait anxiety has been linked to enhanced differential amygdala reactivity during early (Sehlmeyer et al., 2011; Barrett and Armony, 2009) and late (Sehlmeyer et al., 2011) extinction as well as reduced activation in the dorsal anterior cingulate cortex during late extinction (Sehlmeyer et al., 2011). These results are however limited as both studies have acquired fMRI without corresponding autonomic or subjective measures of fear and to the use of immediate extinction protocols. Recently, Sjouwerman et al. (unpublished) demonstrated a negative association between trait anxiety and differential amygdala activation during 24h-delayed extinction in two independent samples, suggesting that the role of trait anxiety on extinction processes may critically depend on procedural and mechanistic operationalizations.

In sum, data on fear extinction and return of fear is sparse and future research should be attentive with respect to operationalization of extinction (i.e., delayed vs. immediate extinction) and investigate the impact of trait anxiety on the return of fear more extensively.

4.1.4. State anxiety

Most studies have focused on trait anxiety but evidence suggesting that state anxiety may also be of relevance is emerging. For example during fear acquisition and extinction following anxious, happy or neutral mood induction (and corresponding changes in state anxiety), differential SCRs did not differ depending on state anxiety, whereas general autonomic responsivity was lower during acquisition but higher during extinction in high state anxious individuals (Vriends et al., 2011). In addition, individuals characterized by higher state anxiety showed more pronounced startle context discrimination (Glotzbach-Schoon et al., 2015) but a less pronounced cued CS discrimination in SCRs during reinstatement (Kuhn et al., 2016b).

In sum, despite of a substantial number of negative findings (in mostly small samples employing null hypothesis significance testing however, see Supplementary Table 1), several characteristics of trait anxious individuals have been pinpointed in fear conditioning protocols including enhanced reactivity to dangerous stimuli, deficits in safety signal learning (e.g., CS-, contextual safety), overgeneralization of fear to innocuous stimuli and deficits in cognitively forming associations between an aversive event and predictors thereof (i.e., CS-US contingency), which again may induce global feelings of anxiety. Hence, the assessment of contingency awareness, which is not yet ubiquitously employed (see Supplementary Table 1) is highly recommended in studies investigating the role of trait anxiety on fear conditioning processes (see Lonsdorf et al., 2017 for further details concerning the assessment of contingency awareness). In addition, contextual, also subtle and potentially unintended, manipulations in experimental design deserve extraordinary attention.

Furthermore, previous studies investigating an association between fear conditioning and trait anxiety have employed dichotomous classifications of trait anxiety such as median-split procedures (Kindt and Soeter, 2014; Haddad et al., 2012; Barrett and Armony, 2006), recruitment of extreme groups (Gazendam et al., 2013; Torrents-Rodas et al., 2013; Glotzbach-Schoon et al., 2013b) or dimensional approaches in healthy individuals (Indovina et al., 2011; Haaker et al., 2015; Martínez et al., 2012; Baas, 2013; Baas and Heitland, 2015; Browning et al., 2015; Sehlmeyer et al., 2011). Most dimensional studies however are inherently limited by small sample sizes with few reports exceeding *N* = 60 (Haaker et al., 2015; Baas and Heitland, 2015) as also generally illustrated in Fig. 5. With increasing sample sizes in future studies (see Section 5 for an outlook and suggestion), the

advantages of dimensional approaches (see Section 2) should be used more readily.

In addition, as evident from Fig. 3A and B, studies employing categorical analyses (i.e. median split, recruitment of extreme groups) vary substantially in both the mean STAI trait score in groups assigned to high and low anxious as well as the difference between both groups. Similarly, studies on the role of trait anxiety in general and fear conditioning processes show a wide range of mean STAI trait scores across studies (see Fig. 3C). Together, this may significantly hamper replication of findings across studies and future work needs to consider these details when discussing new findings on the background of previous findings.

Finally, some studies report findings to be specific for cognitive measures (i.e. ratings of fear and US expectancy; Kindt and Soeter, 2014; Haaker et al., 2015) or read-out measures that are thought to tap into more affective processing such as FPS (Gazendam et al., 2013; Glotzbach-Schoon et al., 2013b). In our view, there is not enough evidence to conclude a systematic and specific impact of trait or state anxiety on specific read-out measures (see also Section 2.1) and future investigations should fill this gap by employing a multimodal approach to capture different response levels and establish boundary conditions.

4.2. Neuroticism

Neuroticism refers to the tendency to express negative affect that has been shown to be a robust predictor of (affective) psychopathology (see e.g., Ormel et al., 2013; Watson et al., 2005). Individuals scoring high on neuroticism are more likely to experience anger, envy, guilt, and depressed mood as compared to those scoring low on neuroticism and are emotionally more reactive and vulnerable to stress. In general, measures of neuroticism combine items referring to negative affect in general, anxiety, worry, anger, frustration, hostility and irritability. Interestingly, neuroticism has been linked to reactivity of brain areas implicated in fear conditioning processes such as the amygdala, the hippocampus and prefrontal areas (for a review see Ormel et al., 2013), making this construct a theoretically interesting candidate.

The majority of studies have not observed a significant association between neuroticism and (differential) fear acquisition processes in samples as large as 217 individuals (Pineles et al., 2009) using SCRs (Otto et al., 2007; Fredrikson and Georgiades, 1992; Pineles et al., 2009; Martínez et al., 2012; Hur et al., 2015; Tzschoppe et al., 2014), ratings of arousal, contingency (Tzschoppe et al., 2014), valence (Tzschoppe et al., 2014; Arnaudova et al., 2016) or US expectancy (Lommen et al., 2010; Arnaudova et al., 2016), heart rate measures (Fredrikson and Georgiades, 1992), avoidance behavior (Arnaudova et al., 2016) and BOLD fMRI responses (Tzschoppe et al., 2014).

The positive findings reported in the literature provide a heterogeneous picture with little converging and convincing evidence as most findings were restricted to very specific boundary conditions that have however not been investigated systematically: A steeper decline in CS + responding (but not CS- or differential responding) over acquisition trials was however linked to low self-consciousness, a subfacet of neuroticism (N4; Pineles et al., 2009). Furthermore, the impact of neuroticism has been shown to depend on the availability of executive resources as overall stronger differential acquisition was only observed in individuals high in neuroticism under low executive load (Hur et al., 2015). On the neural level, a positive association between neuroticism and activation of the amygdala and hippocampus during (observational) fear acquisition was observed in a small sample of twelve young adults (Hooker et al., 2008). High levels of neuroticism were, despite of null findings in physiological, rating and BOLD fMRI measures, linked to a stronger interaction (i.e., as assessed by PPI) between the amygdala and the hippocampus as well as between the amygdala and prefrontal (i.e. ventromedial and dorsolateral) areas and the anterior cingulate cortex during differential (i.e., CS + > CS-) fear acquisition (Tzschoppe et al., 2014).
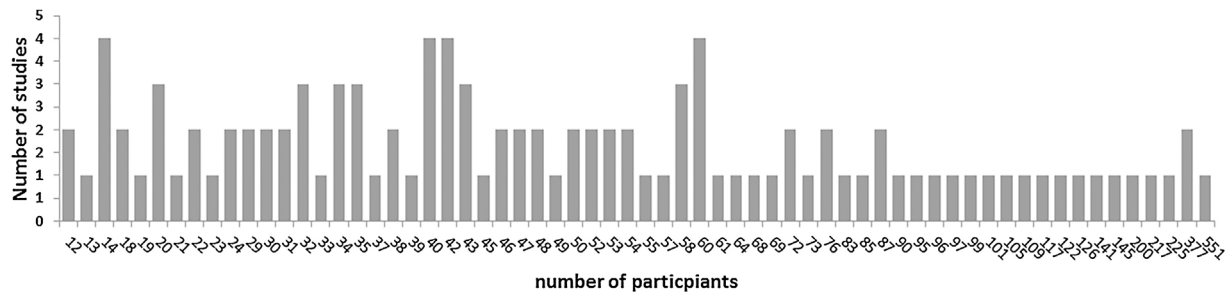
Fig. 5. Number of participants [range: 12–551, mean (SD): 66.2 (76.8)] in studies on inter-individual differences in fear conditioning (as derived from Supplementary Table 1). Publications that report multiple substudies are considered separately.

However, nearly all of these studies performed to date employed a 100% reinforcement rate (Otto et al., 2007; Fredrikson and Georgiades, 1992; Pineles et al., 2009; Hur et al., 2015; Arnaudova et al., 2016) and this proportion is relatively higher as compared to studies on trait anxiety and fear acquisition for instance (see Fig. 2A). Hence, it can be speculated that the study design might not allow for an optimal manifestation of inter-individual differences in conditioning performance (see Section 2.1). Despite more ambiguous experimental situations induced by fear generalization, experimental tests also revealed no impact of neuroticism on fear generalization gradients as assessed by ratings of US expectancy and valence as well as SCRs and FPS (Arnaudova et al., 2016), whereas individuals high in neuroticism showed more avoidance of ambiguous (i.e., generalization stimuli) during fear generalization as compared to individuals low in neuroticism (Lommen et al., 2010).

Similar to fear acquisition, null findings for extinction were observed in SCRs (Fredrikson and Georgiades, 1992; Pineles et al., 2009; Tzschoppe et al., 2014), ratings of arousal, contingency and valence (Tzschoppe et al., 2014), heart rate measures (Fredrikson and Georgiades, 1992) and BOLD fMRI responses (Tzschoppe et al., 2014).

4.2.1. Summary and suggestion for future studies

Evidence speaking in favor of an association between neuroticism and fear acquisition, extinction and generalization processes is to date very limited. It has however to be noted that few studies employed paradigms promoting weak experimental situations and few studies have acquired physiological measures of conditioned responding to date. Similarly, work on the return of fear is absent. Hence, even though the currently available evidence does not suggest inter-individual differences in neuroticism to play a major role in fear conditioning processes, a substantial number of questions remain unanswered (see also Section 4.4 for a general discussion on trait variables in fear conditioning).

4.3. Intolerance of uncertainty

Intolerance of uncertainty (IU) is defined as a dispositional tendency to interpret ambiguous situations as threatening (i.e. cognitive bias) and is considered a critical *trans*-diagnostic factor for anxiety and depression (Carleton, 2012; Carleton et al., 2013; Gentes and Ruscio, 2011; Grupe and Nitschke, 2013; McEvoy and Mahoney, 2012; Whalen, 2007). Hence, with respect to fear conditioning processes, a specific impact on inherently uncertain and ambiguous situations (uninstructed learning, extinction, return of fear, fear acquisition with low reinforcement rate or multiple CSs, see 2.1) might be expected.

4.3.1. Fear acquisition, fear expression and generalization

In line with this hypothesis, no impact of IU on differential SCRs were reported in studies employing a 100% reinforcement rate during fear acquisition (Morriss et al., 2016b; Morriss et al., 2015). In turn, a negative association was found between IU scores and startle responding during uncertain but not during predictable threat conditions

or general startle responding in a modified NPU-threat (threat of predictable and unpredictable aversive events) test (Nelson and Shankman, 2011). Similarly, IU correlates with differential FPS during fear acquisition with 50% but not 75% reinforcement ratio (Chin et al., 2016) and a study employing a 50% reinforcement ratio and including additional generalization stimuli showed gradual discrimination in SCRs following perceptual similarity to the CS+ in the low, but not the high IU group which showed identical responses to all CSs (Morriss et al., 2016a). As hypothesized above, this might be explained by more ambiguity inherent in the fear generalization design which may allow inter-individual differences to manifest more easily (see 2.1). In line with this, prospective IU (indicative of cognitive concerns about future events) but not inhibitory IU (indicative of behavioral inhibition or avoidance) was linked to attenuated late positive potentials to generalization CSs in an instructed fear paradigm, which may indicate differences in elaborate processing of motivationally salient information between high and low IU individuals (Nelson et al., 2015).

Despite these promising findings a study using a low (i.e., 33%) reinforcement rate (Dunsmoor et al., 2015) did not observe an association of IU scores with fear conditioning performance (SCRs). The employment of salient angry faces as CSs (as compared to neutral geometric shapes by Morriss and colleagues (2016) as well as the exclusion of participants failing to show conditioned SCRs above a certain criterion (see 2.1) might explain these discrepant results. Yet, a second study designed explicitly to generate an ambiguous learning situation also failed to observe an association between IU scores and ratings of valence and US expectancy during complex fear learning procedures (Arnaudova et al., 2013). Hence, the available evidence suggests a possible impact of IU on fear acquisition particularly in ambiguous situations although boundary conditions under on which this association might be contingent on are not yet clear.

4.3.2. Extinction and return of fear

During immediate extinction following fear acquisition with 100% reinforcement, significant CS+/CS- discrimination during early extinction was only observed in the low IU group, while at the end of extinction it was only evident in the high IU group (Morriss et al., 2016b; Morriss et al., 2015). Converging, a negative correlation between IU scores and differential amygdala activation was observed during early extinction whereas during late extinction, a positive correlation between IU scores and differential amygdala as well as activation of the vmPFC was observed (Morriss et al., 2015). The relevance of these findings as well as the relation between IU, autonomic and neural indicators of CS-discrimination, including possible mediation effects however remain unaddressed to date.

Additional evidence derived from immediate extinction following more ambiguous acquisition protocols (i.e., lower reinforcement rate) suggests a gradual CS discrimination following perceptual similarity to the CS+ in SCRs only in individuals with high IU (Morriss et al., 2016a) as well as a positive association between differential SCRs and IU scores was observed during spontaneous recovery (Dunsmoor et al., 2015).

In sum, evidence suggesting an association between fear extinction

processes and IU is to date limited due to the use of immediate extinction protocols and some interesting findings that are however not yet converging into a clear picture. These results need to be replicated and extended in the future − in particular as these findings nearly exclusively originate from one laboratory.

4.3.3. Summary and suggestion for future studies

Results from experimental fear conditioning and extinction are generally in line with studies from affective (threat) processing demonstrating correlations between IU scores and activation of the amygdala, prefrontal areas (Schienle et al., 2010) and the anterior insula (Shankman et al., 2014; Simmons et al., 2008). Importantly, the impact of IU on CRs mainly manifested in autonomic responding (Morriss et al., 2016a; Morriss et al., 2016b; Morriss et al., 2015; Dunsmoor et al., 2015) and neural activation (Morriss et al., 2015), whereas ratings of uneasiness generally seem less sensitive to the impact of IU (Morriss et al., 2016a,b; Morriss et al., 2015). Furthermore, specificity of the findings to IU as compared to trait anxiety and worrying, which share a substantial amount of variance (Morriss et al., 2016b), suggest a rather specific effect of IU beyond trait anxiety (Chin et al., 2016; Morriss et al., 2015; Dunsmoor et al., 2015), worrying (Nelson and Shankman, 2011; Morriss et al., 2016a), neuroticism or anxiety sensitivity (Simmons et al., 2008), even though unpublished data from our group in a substantially larger sample (N = 288) suggest an impact of trait anxiety on CS-discrimination during fear acquisition beyond IU despite a significant impact of both constructs when analyzed in isolation (Sjouwerman et al. unpublished).

Taken together, preliminary evidence suggests that IU may be linked to inter-individual differences in the ability to discriminate threat and danger particularly under ambiguous circumstances, which has been suggested to be mediated through perceived control over anxiety-related events (Nelson and Shankman, 2011) and cognitive flexibility (Lieberman et al., 2015). Associations between fear acquisition and extinction processes and IU, albeit preliminary, seem in line with studies suggesting a causal role of IU in pathological anxiety and a decrease in IU following cognitive behavioral therapy (CBT; Boswell et al., 2013). As a consequence, it might be speculated that enhancing tolerance to uncertainty through training programs (Ladouceur et al., 2000) might represent a promising avenue for clinical prevention and intervention of anxiety symptoms.

4.4. Interim summary: trait variables

Taken together, several conclusions can be derived from the above narrative review of associations between trait variables and fear conditioning processes. First, there is at least some evidence suggesting an association between several traits or cognitive biases linked to negative emotionality and fear conditioning processes. In other words, traits might predict fear conditioning performance (i.e. contribute to noise reduction relative to signal). (Preliminary) evidence suggests that such a link does indeed exist but the facet of negative emotionality at the core of this association has not yet been pinpointed comprehensively. For instance, few studies (Chin et al., 2016; Morriss et al., 2015; Dunsmoor et al., 2015; Sjouwerman et al.,unpublished) have investigated the specificity of their findings to a single trait variable over and above other related and correlated constructs of negative affect. Additionally, it has been noted that despite of reporting the assessment of multiple questionnaires assessing various trait markers of negative emotionality in the methods section, reported results are often restricted to a single trait variable (see Supplementary Table 1). Often negative findings are only briefly mentioned in the results but cannot be extracted from the abstract which hampers their recognition. This raises concerns about possible reporting bias, undisclosed 'researcher's degree of freedom' and hence potentially false positive reports in the field (Simmons et al., 2011) as negative findings are often 'hidden' as a side-note in a positive report focusing on a different trait variable or

research question. Hence, progress is currently hampered by a substantial amount of noise induced by study design, reporting and analysis. It becomes also clear that much evidence on inter-individual differences in fear conditioning processes are derived from studies whose primary aim was a different research question, again raising concerns about reporting biases and potential multiple testing. Thus, future studies are recommended to pursue a multidimensional approach assessing different facets of negative emotionality and applying appropriate and innovative statistical methods to identify the unique characteristics at their intersection that is associated with fear conditioning processes. It is absolutely conceivable that different subprocesses of fear conditioning might be affected by different traits and their potentially non-additive interactions (Gazendam et al., 2014) and that this link might be additionally moderated by contextual and procedural factors (i.e., boundary conditions, see Fig. 4). Evidence based on the limited number of available studies that have not systematically addressed specific questions to date however precludes clear-cut conclusions.

Second, findings across and within specific trait variables are difficult to reconcile as there is no clear picture emerging with respect to differential sensitivity of specific read-out measures of conditioned responding, which again might depend on procedural specifics (e.g., reinforcement ratio) in combination with specific fear conditioning processes targeted by experimental design.

Third, as evident from Fig. 3A, the mean score of individuals labeled as 'high' or 'low' in a certain trait variable does not necessary converge (discussed in Section 2). Thus, interpretability and comparability across studies is significantly hampered. Similarly, mean scores in the sample differ widely posing similar interpretation difficulties, in particular when not reconciling experimental details of very individual study. Future studies should thus focus on dimensional analyses to circumvent costs of dichotomizing continuous variables (see Section 2.2).

Fourth and finally, despite the theoretical plausibility of weaker situations allowing for an optimal manifestation of inter-individual differences, experimental work testing this hypothesis (e.g., by employing different reinforcement rates) has not yet been addressed. Such methodological work is eagerly awaited.

5. The story of noise evolving into a meaningful tune: inter-individual differences

Following from the above described associations between inter-individual difference factors and fear conditioning processes it has become clear that inter-individual difference variables carry meaningful and potentially highly valuable information (i.e., 'signal'). What has been regarded as noise in the past is suddenly at the center of attention and steadily developing into a meaningful, albeit complex, tune.

On the other hand, it is clear that the field is still in its infancy. More precisely, the recent paradigm shift from a focus on average responding to the investigation of inter-individual differences has generated only a limited number of studies and hence evidence on a particular inter-individual difference variable does often not yet converge into a crystal clear picture. In addition, studies have to date nearly exclusively relied on measures of central tendencies and studies employing methods (see methodological discussion in Ozomaro et al., 2013) specifically suited for the investigation of individual differences (in trajectories) are emerging only very recently (for examples see Galatzer-Levy et al., 2017; Gazendam et al., 2014). Nevertheless, the available evidence provided here in combination with methodological discussions should motivate systematic investigations specifically tailored towards the investigation of inter-individual differences in fear conditioning processes and employing rigorous, targeted and innovative statistical approaches (see also considerations in Section 2) in large sample sizes to make fully use of the field's potential. In addition, the predictive validity of the identified inter-individual difference factors for clinically relevant aspects need to be addressed providing an important next step.

Importantly, a number of different but however not mutually exclusive multi-deterministic mechanisms (illustrated schematically in Fig. 4) can be extracted from our literature overview that might converge to a final common pathway of predisposing an individual to ex-aggerated fear and anxiety. These mechanisms include for instance 1) elevated threat signal processing, 2) reduced safety signal processing, 3) deficits in discrimination signals of danger and safety, 4) deficits in CS-US contingency awareness, 5) broadened fear generalization, 6) lack of habituation, 7) deficits in or enhanced consolidation of extinction and fear memory respectively and 8) deficits in or enhanced retention of extinction and fear memory respectively (see Fig. 4). Disentangling and dissociating the exact mechanism(s) and most critically their interactions as well as contextual and procedural boundary conditions that predisposes a certain subprocess in fearful behavior not only requires experimental designs tailored towards this specific subprocess but may also enhance our understanding of the etiology and classification of different mental disorders and as such contribute to the RDoC initiative (Insel, 2014; Cuthbert, 2014 Cuthbert, 2014).

Moreover, any inter-individual difference factor may exert its effect on multiple of these different mechanistic levels and in interaction with any other inter-individual difference factor. Hence, multiple routes to pathological fear and anxiety exist in different individuals that might share a final common pathway: increased risk to develop an anxiety disorder. Unraveling these individual risk profiles hence holds strong clinical potential for the development of targeted prevention and intervention approaches in the future (for an example from alcohol misuse see Conrod et al., 2013). The descriptive model depicted in Fig. 4 may serve as a starting point to motivate hypotheses and design research programs specifically tailored to inter-individual difference research in the field of fear conditioning. Importantly, results from the above mentioned experimental studies in healthy participants line up with studies in patients (for a metaanalysis see Duits et al., 2015) pointing to similar mechanisms, which highlights the translational value of this research area.

Pinpointing and delineating the role of inter-individual difference factors as well as their interaction in fear conditioning, extinction and return of fear processes requires large sample sizes − a fact that stands in sharp contrast to the number of participants included in studies on inter-individual differences in fear conditioning processes to date (see Supplementary Table 1). As evident from Fig. 5, only a minority of studies have included total sample sizes larger than 60 – the number of participants per group being even substantially smaller. As a consequence, we have to set the next stage of this research field by employing rigorous methods and potentially by research groups joining collaborative forces beyond the capability of individual researchers and individual funding. As such multi-methodological, multi-site data pooling protocols cross-cutting disciplines (i.e., different 'units of analysis') and geographical borders (which might have an impact in itself) have to emerge and optimally be complemented by the initiation of large scale data sharing networks and complementary research across groups. In addition, in order to gain larger sample sizes and promote generalizability, recruitment strategies should be reconsidered as well (see Section 2.1). Thus, results should not be restricted to recruitment of primarily (psychology) students, but also include participants from the general public and a wider age range allowing for more variance in the data. Widening the recruitment strategy might also lead to larger sample sizes within one location, complementing the multi-site data pooling approach. These proposed changes will provide us with unprecedented opportunities to bring significant advances in the field and mechanistic insights within reach − finding true signal in the noise.

As a pre-requisite, a consensus must be reached with respect to data acquisition (e.g., identical experimental protocols, formulation of questions for ratings), inclusion of relevant information beyond conditioned responding itself (such as CS-US contingency awareness), data processing and quantification of conditioned responding, which again requires researchers to join forces and agree on fundamental questions,

an attempt that the '*Research Network for the European Interdisciplinary Study of Fear and Extinction Learning as well as the Return of Fear (EIFEL-ROF)*' is striving at (Lonsdorf et al., 2017). Complementary methodological, computational and technical advances, such as mediation analyses, multivariate pattern analyses within machine learning approaches or latent growth models can be expected to foster such endeavors and allow for translation of basic research findings to the clinics as single-subject predictions (Lueken et al., 2016; Pine, 2016).

As such, in the future, synergistic cooperation cross-cutting the fields of psychology, molecular genetics, neuroimaging, neuroinformatics, psychophysiology, and psychopharmacology will not only improve our mechanistic understanding but can also be expected to generate multimodal risk profiles contributing to the development of specifically tailored ('individualized') behavioral and pharmacological intervention and targeted prevention programs in the future. This approach holds potential to provide us with the still missing pieces of the puzzle to fully capture the complex meaning of the evolving inter-individual differences tune in fear conditioning research.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2017.07.007.

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