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Review article

Don't fear 'fear conditioning': Methodological considerations for the design and analysis of studies on human fear acquisition, extinction, and return of fear

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ABSTRACT

The so-called '*replicability crisis*' has sparked methodological discussions in many areas of science in general, and in psychology in particular. This has led to recent endeavours to promote the transparency, rigour, and ultimately, replicability of research. Originating from this zeitgeist, the challenge to discuss critical issues on terminology, design, methods, and analysis considerations in fear conditioning research is taken up by this work, which involved representatives from fourteen of the major human fear conditioning laboratories in Europe.

This compendium is intended to provide a basis for the development of a common procedural and terminology framework for the field of human fear conditioning. Whenever possible, we give general recommendations. When this is not feasible, we provide evidence-based guidance for methodological decisions on study design, outcome measures, and analyses. Importantly, this work is also intended to raise awareness and initiate discussions on crucial questions with respect to data collection, processing,

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Individual differences
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statistical analyses, the impact of subtle procedural changes, and data reporting specifically tailored to the research on fear conditioning.

Contents

The so-called '*replicability crisis*' (Open Science Collaboration, 2012, 2015; Stroebe and Strack, 2014) has sparked methodological discussions in many areas of science in general, and in psychology in particular. This has led to recent endeavours of the scientific community to promote the transparency, rigour, and ultimately, replicability of research.

Originating from this zeitgeist, the challenge to discuss critical issues on terminology, design, methods, and analysis considerations in fear conditioning research has recently been taken up by the '*Research Network for the European Interdisciplinary Study of Fear and Extinction Learning as well as the Return of Fear (EIFEL-ROF)*'. Strong intest in this research field is demonstrated by a massive increase of publications in the field from about 15 publications per year in the 1990ies to over 300 per year in recent years (Source: Scopus). This increase in research on fear conditioning has however been accompanied by a proliferation of applications of the basic model with different design and methodological variations, calling for methodological discussions. After almost a century of research since the publication of the first work on human fear conditioning (Watson and Rayner, 1920), a group of (young) scientists have met on a regular basis since May 2015, to identify and debate on urgent open questions and important methodological considerations. This endeavour originated from and is reflective of the spirit of the annual European Meeting on Human Fear Conditioning (EMHFC). The present work represents the brainchild of these discussions that involved representatives from fourteen differnt laboratories working on human fear conditioning in Europe.

The objective of this work is twofold. *First*, we aim to provide a tutorial for novices with respect to terminology, design, and analysis considerations, including a critical evaluation of read-out measures, their applicability and usage in human fear conditioning research. Many of these methodological considerations have been discussed intensively among experts in the field but are not easily accessible to laboratories new to fear conditioning research or students. *Second*, we wish to contribute to methodological coherence and transparency by making suggestions on experimental design, data collection, processing, statistical analyses and what to report when publishing fear-conditioning data. The latter aim is critical in light of the ongoing debate on 'undisclosed flexibility in data collection and analysis' (cf. Simmons et al., 2011). Thereby, we intend to raise awareness regarding the consequences of subtle procedural changes in the to-be studied process. In sum, this compendium intends to provide a basis for the development of a common procedural framework for the field of human fear conditioning and to provide encyclopaedic guidance for methodological decisions on design and analysis. We provide general recommendations whenever possible. Whenever methodological decisions depend on the specific research questions, aims and sample characteristics, we provide evidence-based guidance for methodological decisions by compiling factors influencing the specific outcome. Thereby, we hope to spark fruitful discussions and renew interest in methodological research to ultimately establish a consensus in the field with respect to design and analysis.

Before however going into methodological details, we set out with a brief primer on different aspects of fear conditioning and extinction procedures and terminology, to provide solid ground for procedural discussions. Importantly, we explicitly do not aim to review theories, mechanisms and general findings in the field, but will refer to other relevant sources whenever appropriate.

1. A brief primer on fear conditioning procedures and terminology

Nearly a century ago, the advent of fear conditioning research in humans was marked by the historical experiment with little Albert, who was made to fear a rat by pairing it with a loud startling noise (Watson and Rayner, 1920). The experimental model of fear conditioning model was derived from the more general conditioning model developed by Ivan Pavlov (1927), who initially studied appetitive conditioning processes.

To date, one of the unique features of the fear conditioning model remains its excellent translational value (however, for cross-species translational considerations see Table 1), both from rodents to humans and onwards to clinical populations and back. Animal experimental work provides a richness of inspiration for translational studies for human behavioural (neuro)scientists and there is a wealth of information available today derived from animal experiments on the behaviour, neurobiology and pharmacology of the acquisition (Davis et al., 1993; LeDoux, 2000), extinction (Bouton et al., 2006a,b; Myers and Davis, 2002; Quirk et al., 2006), and return (Bouton, 2002; Vervliet et al., 2013b) of fear responses.

However, translational research across species always bears inherent theoretical and methodological limitations, a comprehensive discussion is, however, beyond the scope of this work. Table 1 provides an outline of methodological comparisions between fear conditioning procedures in animals (rodents) and humans. The theoretical challenges have been discussed in detail elsewhere (e.g. for the acoustic startle response see Fendt and Koch (2013); for fear extinction see Milad and Quirk (2012), for fear acquisition and extinction across development see Shechner et al., 2015; for disparities between affective and cognitive neuroscience in general see Panksepp et al., 2017; for fear vs. threat responses see LeDoux, 2012; LeDoux and Pine, 2016).

Fear conditioning processes are considered critical in the pathogenesis and maintenance of pathological anxiety. In line with this idea, deficits in fear conditioning processes have been demonstrated in patients with anxiety disorders (Duits et al., 2015; Lissek et al., 2005a,b). Thereby, the development, treatment, and relapse of pathological fear can be modelled experimentally by using fear acquisition, extinction, and return of fear (ROF) paradigms respectively. All of these aspects fall under the umbrella term of 'fear conditioning'. As terminology in the field is not clearly defined and, at times, used ambiguously, we set out with precisely defining relevant technical terms for this work (see Table 1) before proceeding to methodological discussions.

A fear conditioning experiment commonly consists of different experimental phases. ***Acquisition*** of conditioned fear (see 3.2 for details) is achieved by presenting a stimulus (conditioned stimulus, CS+) paired with an aversive event (unconditioned stimulus, US), a procedure referred to as ***fear acquisition training***. As a result of this pairing, ***fear learning*** takes place, manifesting in the development of ***conditioned responses*** (CRs) to the CS. These CRs include fear, orienting, or defensive responses.

Fear acquisition represents, in principle, an adaptive process critical to survival in dynamic environments. However, behavioural flexibility is of equal importance, as behaviour should no longer be guided by a CS that has lost its predictive value with respect to the US. This process is modelled by presenting the CS in absence of the US (***extinction training,*** 3.4 for details). The result of this procedure is typically a decrement in the CR triggered by the CS, referred to as (within-session) ***extinction learning***. Extinction is considered the central mechanism in the cognitive-behavioural exposure-based treatment of pathological fears (Rachman, 1989).

Clinical and experimental observations show that upon re-confrontation with a CS at a later time, (***retention test***) the extinction memory is not always expressed (***extinction retention***). On the contrary, often a re-occurrence of conditioned responding (***ROF expression***) is observed.

Importantly, the contemporary view on extinction is that the original conditioned fear memory trace is not erased, but a competing (inhibitory) extinction memory trace is formed (Bouton, 2004;

Table 1
Considerations for cross-species translation of rodent and human work.

	Rodent work	Human work
Conditioned stimulus type	Auditory tones, olfactory, and visual cues (e.g. lights)	Mostly visual cues (geometric shapes, faces, objects, and lights), rarely auditory or olfactory
Outcome measures	% time freezing, (whole body) fear-potentiated startle,[a] avoidance, operant elements (bar presses for food), and electrophysiology	Fear-potentiated startle (eye blink), skin conductance responses, heart rate, pupil dilation, blood-oxygen-level-dependent (BOLD) contrast in functional magnetic resonance imaging (fMRI), electroencephalography, magnetencephalography, avoidance behaviour and verbal reports
Focus of outcome measures	Fear *behaviour* (freezing and avoidance)	Pychophysiological responses, BOLD, and subjective verbal reports
Conditioning protocol	Mostly single-cue, sometimes differential Multiple day experiments allowing for consolidation between experimental phases	Mostly differential, rarely single-cue Mostly single day experiments with multiple day experiments becoming more popular
Context in the cued fear test	In a novel context (as in single-cue studies, no control CS is available)	Novel context not necessary because of the differential design
Operationalization of the context	Different cages (and odours)	Background stimuli on a computer screen, separate rooms, virtual reality, and odours
Fear acquisition training	Usually spread over multiple sessions (on a single day) or multiple days, often based on a criterion	Mostly single session, rarely limited to a criterion, sometimes instructed about contingencies
Unconditioned stimuli	- Typically non escapable - Intensity identical for all animals (non-calibrated and not experienced previously) - typically foot shock	- In principle, avoidable (ethic constraints; experiment may be aborted) - Intensity of electrical stimulation that is individually calibrated (i.e. experienced prior to the fear acquisition session) - Electrical stimulation to finger, wrist or shin, aversive tone, human scream, and air blast
Reinforcement rate	100% or partial (<100%)	100% or partial (<100%)
Contextual change between experimental phases (acquisition training, extinction training, and retention test)	Common	Sometimes
Between session experiences (e.g. food)	Controlled for	Usually uncontrolled
Situational factor	Real-life threat situation	Artificial experimental situation
Population	Mostly inbreed strains or littermates	Typically non-related volunteers (i.e. possibly pre-selection), often student populations as healthy participants

[a] This includes a matching a procedure a couple of days prior to acquisition training to ensure similar baseline levels of sensitivity to the startle probe in animals, which is not commonly done in humans.

Myers and Davis, 2007). Several procedures (referred to as ***ROF manipulations,*** see 3.5 for details) have been developed to induce the process of ***ROF*** by experimentally manipulating the dominance of the fear memory trace over the extinction memory trace. This is tested using a ***ROF test phase,*** which is procedurally similar to a retention test and can be achieved through contextual change (renewal), re-exposure to the US or another aversive event (reinstatement) or the mere passage of time (spontaneous recovery; see 3.5 for details).

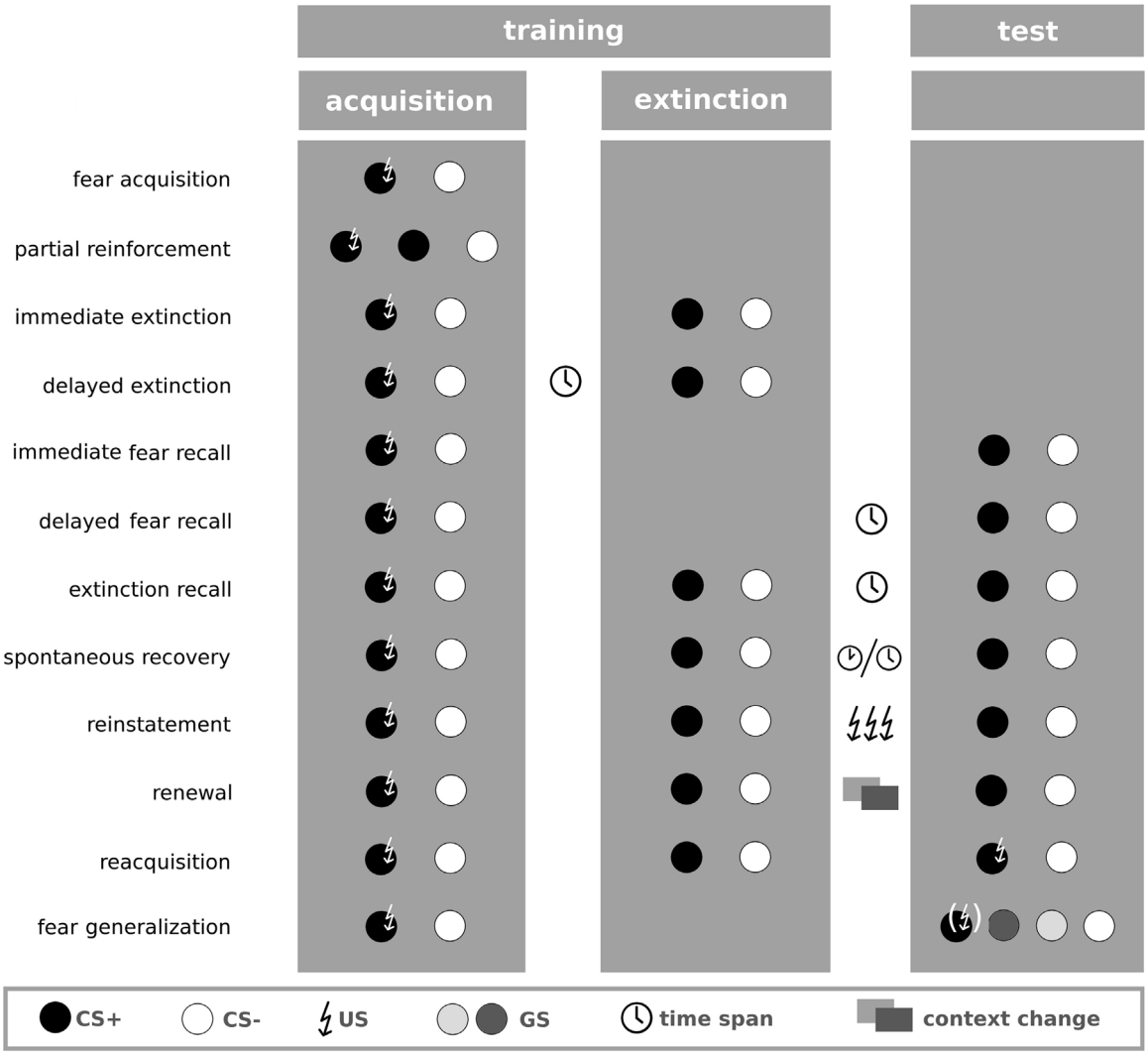
These procedures represent experimental models in which putative mechanisms for relapse after successful extinction-based therapy can be studied (Bouton, 2004; Craske et al., 2008; Rachman, 1989; Vervliet et al., 2013b). As the focus of this paper is of methodological nature, we will not discuss theoretical considerations regarding the mechanisms in the following, unless relevant for methodological reasons.

2. Elements of a conditioning protocol and experimental variations

Different laboratories in thefield have established different routines regarding the details of the conditioning protocol, outcome measures, data processing, and analysis. This results not only in a daunting number of choices when setting up a fear conditioning experiment, but also represents a challenge for comparing data across labs. To date, the field lacks clear methodological recommendations as well as a comprehensive discussion and compilation of methodological and design choices, a gap that the present work starts to bridge.

Thereby, we will focus on basic variants of Pavlovian or classical conditioning paradigms commonly employed in the human field, and discuss critical experimental design and analyses choices for different experimental phases. Readers are referred to other sources for more specialized work on theoretical accounts (Gallistel, 2004), alternative pathways for the acquisition of fear such as observation and instruction (Mechias et al., 2010; for a review see Olsson and Phelps, 2007; for an observational fear conditioning protocol see Haaker et al., 2017; Rachman, 1977), procedures such as operant protocols and transfer of Pavlovian to instrumental conditioning (Beckers et al., 2013; Krypotos et al., 2015) and reconsolidation (see Agren, 2014; Fernández et al., 2016; Meir Drexler and Wolf, 2016 for reviews including methodological discussions).

Table 2
Prototypical (cue) training and test procedures in fear conditioning studies illustrating procedural differences and similarities across different operationalizations (see Table 1 for terminology). The Table also serves to illustrate that identical procedures are referred to by different terminology based on the study aim (see below for details).



During *fear acquisition* training (first row), a CS (CS+, black dot) predicts the occurrence of an US (bolt) while a control stimulus (CS-, white dot) does not (differential protocol; see 3.2.1). Reinforcement rate can thereby vary between 100% (continuous; first line) or less than 100% (partial; second line, see **2.2.1**). Further variations such as number of trials and CS-US timing are described in the text (see **2.2**).
Extinction training can take place immediately after (third row) or after a temporal delay (fourth row) following acquisition training and includes a test of the CR in itself (i.e. immediate and delayed extinction might also be illustrated in the 'test' column). Similarly, *fear recall* can be assessed immediately after (fifth row) or after a temporal delay (sixth row) following fear acquisition training. It becomes clear from this example that immediate extinction and immediate fear recall as well as delayed extinction and delayed fear recall theoretically refer to different processes (as illustrated by different positioning in the table) but are operationalized by identical procedures.
A test for *extinction recall* and return of fear (ROF) due to spontaneous recovery involves a test after some passage of time (in case of spontaneous recovery tested at different time-points), whereas other *ROF phenomena* (reinstatement, renewal and rapid reacquisition) can be observed after an active post-extinction manipulation (reinstatement US presentation, contextual change or new CS-US pairings) as described in **3.5**.
A *fear generalization* test typically takes place following fear acquisition training and involves presentations of the CS-, similar stimuli (generalization stimuli, GS), as well as reinforced and/or non-reinforced presentations of the CS+ (see **3.3**).

In the following sections, we provide a compilation of elements included in studies on human fear conditioning with a focus on methodological considerations. These considerations are important for guiding informed choices of experimental stimuli and procedural variations. Importantly, different procedures might engage different processes ultimately causing different results. This leads to confusion when methodological differencens are not adequately reflected in the terminology (see Table 2) and discussion of the results.

Furthermore, we strongly recommend that authors carefully describe the procedural choices made (for guidance on what to report see Table 5), provide a rationale, and adhere to appropriate terminology for the description and interpretation of their findings (e.g. fear learning vs. fear expression, see 2.2.4).

2.1. Types of stimuli, inter-trial intervals and inter-stimulus intervals

Different types of stimuli are employed in fear conditioning studies, which will be described in detail in the following sections, including their timing as well as number of presentations.

2.1.1. Conditioned stimuli

CSs elicit a CR by virtue of (repeated) pairings with and hence predicting the occurrence of a US. Discrete cues and contexts (see 2.1.2) or a combination of both (see 3.2.4) can serve as CSs. Typically, but not necessarily, a CS is emotionally neutral prior to fear acquisition.

The majority of fear conditioning studies rely on discrete exteroceptive cues, mostly visual CSs, such as pictures of differently coloured lights, geometric shapes (Meulders et al., 2012; Vervliet et al., 2010a,b), human faces, or animals (Hermans et al., 2002). In addition, auditory, tactile, olfactory, and taste CSs have been employed. Recently, proprioceptive CSs such as joystick arm movements (Meulders et al., 2011, 2013, 2015; Meulders and Vlaeyen, 2013) and interoceptive CSs (for a review see: De Peuter et al., 2011) such as respiratory loads (Pappens et al., 2013), oesophageal balloon distension (Zaman et al., 2015), and inhalation of CO_2-enriched air (Acheson et al., 2007) have been applied in pain-related and panic-related fear conditioning research.

Generally, the strength of the CR is also affected by the salience of the CSs. Physically intense or psychologically relevant stimuli are typically more salient and responses to such CSs will show a steep acquisition curve and habituate slowly in rodents (Rescorla and Wagner, 1972). Particular salient stimuli are categories of fear-relevant stimuli such as spiders, snakes, angry faces, or outgroup faces, which are not emotionally neutral prior to conditioning. Generally, fear-relevant CSs have been suggested to lead to faster fear learning and resistance to extinction learning as compared to fear-irrelevant stimuli such as flowers, mushrooms, and happy faces (Mineka and Ohman, 2002; Ohman and Mineka, 2001), a phenomenon that has been coined as 'preparedness'.

Detecting CRs in designs using very intense emotional CSs can be confounded by the ceiling effects of the respective outcome measure. For instance, amygdala activation already inherently increased towards a picture of an angry face may overshadow the discrimination between the angry face serving as CS+ (i.e., the CS predicting the occurrence of the US) and the CS- stimuli (i.e. the CS not predicting the occurrence of the US). In addition, neutral CSs are not perceived neutrally by all participants, for example when human faces used as CSs (e.g., neutral faces might be negatively apprehended in patients with social phobia; Lange et al., 2012). Furthermore, some CS types are disadvantageous in combination with a specific outcome measure, e.g. using auditory CS and fear-potentiated startle (FPS; cf. 4.1.2) or in the loud functional magnetic resonance imaging (fMRI) environment.

2.1.2. Contexts

In addition to the above described discrete stimuli, contextual stimuli have been employed as conditioned contexts. A *context* is defined not only by spatial features, but also by temporal, interoceptive, cognitive, or social aspects of a given situation (for a discussion on the operationalization of contexts in fear conditioning see Maren et al., 2013). Thereby, computer background screens, room illumination, odours, or different physical rooms have been used to create experimental contexts in fear conditioning research (Maren et al., 2013; Urcelay and Miller, 2014). In order to investigate more complex, rich, and ecologically valid contexts in humans, virtual reality paradigms have emerged during the past decade (Baas et al., 2004; Glotzbach-Schoon et al., 2013a,b; Grillon et al., 2006a; Huff et al., 2010).

Notably, subtle changes in the experimental procedure have the potential to induce context-changes such as the passing of time (Maren et al., 2013) or testing within or outside the magnetic resonance (MR) environment (see also 4.1.6). Hence, the conditioning protocol should be carefully controlled for unwanted contextual influences.

2.1.3. Unconditioned stimulus types and intensity

USs signal potential harm to the organism. They innately activate the defensive system, and thereby, elicit an unconditioned response (UR) without requiring previous learning processes. Naturally, pain signals such as electro-tactile stimulation are most commonly employed (for a summary on the role of pain in fear conditioning see Wiech and Tracey, 2013) which represents the application of small, controlled, electric currents to the skin (see also below). However, in clinical populations and young children, a less-aversive airblast to the larynx (e.g. Grillon et al., 2004) as well as auditory stimuli such as loud (white) noise, pure tones, and more complex human screams (Glenn et al., 2012a,b; Hamm et al., 1989) have successfully served as USs. In order to avoid intense physical stimuli as USs, visual stimuli such as pictures from the International Affective Picture System (Lang et al., 2008) or socially relevant USs such as film-clips with critical comments have been applied with mixed results (Pejic et al., 2013; Schweckendiek et al., 2011). Interoceptive USs include, for instance, dyspnea induced through respiratory loads (Pappens et al., 2013), breathing occlusion (Pappens et al., 2012), oesophageal balloon distension (Ceunen et al., 2015), CO_2 inhalation (Acheson et al., 2007; Fannes et al., 2008; Meulders et al., 2010), painful rectal distension (Gramsch et al., 2014; Icenhour et al., 2015; Kattoor et al., 2013), and painful heat stimuli (Jenewein et al., 2013). Thereby, it has to be noted that stimuli from any modality may serve as both a CS and a US depending on their intensity. To improve the ecological validity, the choice of the appropriate US could be made on the basis of the pain modality (Nielsen et al., 2009).

Additionally, meaningful stimulus-stimulus (i.e. CS-US) matches (both on a sematic and sensory level) are more readily acquired and are more resistant to extinction than are mismatches, which has been discussed in terms of their 'belongingness' (Garcia and Koelling, 1966; Hamm et al., 1989). Hence, disorder-relevant USs (De Peuter et al., 2011; Lissek et al., 2008b) may generate stronger associations and CRs.

US intensity is often (particularly in the case of electro-tactile USs) determined individually by assessing the participant's subjective evaluation in a staircase procedure prior to fear acquisition (see 3.1; which is different in rodent work, cf. Table 1). This is of importance, as US salience (associated with US intensity), similar to CS salience, has an impact on the speed of fear learning in rodents (Treviño, 2016), and habituation, which sometimes also leads to sensitization. While this distinction is clear for many US types (e.g. electro-tactile stimulation and aversive noise), emotional pictures are typically not universally threatening and might lead to more individual variance (cf. the 'weak situation' discussed in 5.2).

Since differences in fear learning may derive from differences in US reactivity, we recommend that results do not only contain CR but also UR information, particularly in between-subject designs (see 5.3). However, an appropriate control condition for the US is usually lacking: when nothing follows the CS- this leads to US omission effects (which can be observed for instance in SCRs, see 4.1.1). The typical conditioning experiment does not include a control for the US, possibly because an additional 'non-US' control event after the CS- (Böcker et al., 2004; Klucken et al., 2009; Lissek et al., 2008b) can have unwanted effects on the conditioning processes. For instance, this could add a new association making the learning process consequently more complex. In particular, a non-US event, which is perceived as neutral by all participants, might be difficult to find.

2.1.4. Inter-trial interval and inter-stimulus interval

The inter-trial interval (ITI) in fear conditioning studies refers to the time elapsing between the end of one trial (indicated by stimulus offset, which might be CS or US offset) to the start of the next CS trial (CS onset). Specifically, the ITI has to be conceptually distinguished from the inter-stimulus interval (ISI), which comprises

the interval between CS onset and US onset (Heart, 1988; see 2.2.3). The terms ITI and ISI should not be used interchangeably as this is a source of confusion across labs. Sometimes, also other definitions of ITI and ISI are used, which adds further confusion.

Requirements with respect to the length of ITI and ISI presentations depend critically on the outcome measure of interest (see 4.1.1.1, 4.1.2.1) and on each other. Thus, rather than the absolute ITI or ISI length, the ISI/ITI ratio should also be considered (cf. Heart, 1988). As a rule of thumb, ITI durations should not be shorter than the CS duration in order to avoid backward conditioning (i.e., the subsequent CS coming associated with the US; Hall (1984). Clear guidelines are missing concerning optimal ITI and ISI length, and it is questionable to what extent ITI and ISI length impacts fear conditioning processes (see Cain et al., 2003 for experimental manipulations in mice).

Furthermore, attention should be paid to what is presented during the ITI, as this period might be regarded as a stimulus or context in itself. Sometimes, measurements taken during the ITI are used to contrast the measurements during CS presentations (e.g. when FPS is the outcome measure; cf. 4.2.2). Thus, perceptual resemblance between the conditions that are paired with the US (CS or context) and the ITI should be avoided due to possible generalization effects.

2.2. Procedural variations

2.2.1. Reinforcement rate

Reinforcement rate refers to the probability of US occurrence in the presence of the CS. During fear acquisition training, the CS can be paired with the US on every single trial (100% reinforcement rate; continuous pairing) or in a smaller number of trials only (partial reinforcement). While both procedures generally lead to fear acquisition, partial reinforcement rates in both rodents and humans are not only thought to weaken the development of conditioned responding, but also tend to prolong extinction learning (Bloom and McFarlain, 1971; Dunsmoor et al., 2007; Haselgrove et al., 2004; Hilton, 1969; Schurr and Runquist, 1973). Moreover, in partial reinforcement protocols, reduced response frequency (in humans: Flora and Pavlik, 2013; Galbicka, 1994; Svartdal, 2003; in rodents: Huang et al., 1992) and CR amplitudes (in humans: Dunsmoor et al., 2007; in rabbits and humans: Leonard, 1975) have been reported.

It is important to note that a recent study comparing different reinforcement schedules concluded that partial followed by continuous reinforcement yields the strongest CRs during fear acquisition training, which were also maintained during extinction learning (Grady et al., 2016). Such delayed fear reduction during extinction training is often desirable when extinction is the focus of the experiment, as CRs typically extinguish very rapidly when shifting from 100% reinforcement during fear acquisition training to 0% during extinction training (Vansteenwegen et al., 1998).

Despite considerations concerning the speed of learning, a partial reinforcement schedule is sometimes employed for pragmatic reasons, such as to enable assessment of the response to the CS+ without the (possible) confounding influence of the US presentation, e.g. with fMRI experiments (Büchel et al., 1998a,b; see also 4.1.6.1) or experiments with rapid stimulus-sequences (i.e. short CS and/or ITI durations). Another reason might be to avoid extensive habituation to the US, which is usually set at an individual, but rather mild intensity in humans (cf. Table 2). Note that these practical considerations should be weighed carefully against potentially undesired effects on the process under study.

2.2.2. Trial number and order

Another factor to consider is the number of CS trials. In some protocols, CRs may be observed as rapidly as after one paired trial (e.g., US aversiveness: Ohman et al., 1975), whereas the common number of trials per CS varies between 5 and 20 trials. Usually, the number of presentations is set to be equal for CS+ and CS- to avoid later potential interpretation problems due to differences in learning curves for the different CSs. During extinction, the number of trials is a primary determinant of CR decrement in rodents (Rescorla and Wagner, 1972). For example, it has been shown that many CS trials during extinction training with a duration shorter than the acquisition CS duration facilitated within-session extinction (Golkar et al., 2013a). In retention tests, only a smaller number of trials are needed, since re-emergence of the CRs does not last for a long time due to re-extinction processes. Altogether, the execution of pilot studies to assure an optimal number of trials is recommended when habituation effects in certain response measures (e.g. SCRs, see Section 4.1) or habituation to the US necessitates limiting the number of trials.

Another issue to consider is the CS+ and CS- trial order. Typically, studies use pseudo-random series of CS presentations with the restrictions that no more than two consecutive trials of the same stimulus should occur, and the CS+/CS- proportion is held constant within blocks of trials. This ensures that time-dependent effects, such as habituation, may not bias the comparison between conditions. In addition, if a completely random order is used, there is some risk that fear learning about different CS types that show different CS-US contingencies (i.e. CS+ and CS-) occurs at different speeds. As such, fear learning may be impaired for stimuli that occur relatively late versus early in the series due to the habituation of both CS and US responses. Ordering of reinforced and unreinforced CS+ trials in an experiment with a partial reinforcement rate also warrants further attention: fear learning can start as soon as the first reinforced CS+ trial is presented; thus trial orders with unreinforced CS+ trials occurring at the beginning may generate different learning curves compared to protocols in which the first CS+ trial was reinforced. Additionally, when the series start with multiple unreinforced CS+ trials, the phenomenon of latent inhibition (see also Section 3.1) may hinder fear acquisition. The same applies for the last CS+ trials during the acquisition phase: if the randomization of CS+ and CS- trials result in unreinforced CS+ trials at the very end of the acquisition phase, extinction may in fact start already during the acquisition phase, yielding artificially fast decreases in conditioned responding in the beginning of the (immediate) extinction phase (in humans: Schurr and Runquist, 1973; in rodents: Bloom and McFarlain, 1971; Haselgrove et al., 2004; Hilton, 1969). In addition, the type of the first CS (CS+ or CS-) during fear acquisition training may affect conditioned responding in the subsequent trial. For instance, if the first CS during fear acquisition training is a CS- trial, this is unlikely to affect responding to the next CS trial (e.g. a CS+ trial) while the same may not be true vice versa.

In sum, due to their prime importance, the number of stimuli presented, and in particular, the stimulus order, deserve special attention while designing an experiment.

2.2.3. Conditioned stimulus/unconditioned stimulus timing and duration

As mentioned above, the interval between CS onset and US onset is also referred to as the ISI (Heart, 1988; for a comparison of different ISIs see Öhman, 1974). It should be carefully chosen depending on the outcome measure for the CR (cf. 4.1).

Two elemental designs exist based on the temporal relationship between CS and US: in a *delay conditioning* procedure (i.e. US onset is *delayed* to CS onset), the CS begins before the presentation of the US and continues at least until US onset, while in a *trace conditioning* procedure, the US occurs after a certain time interval after CS offset, called the trace interval (Rescorla, 1988). Trace intervals between 500 ms to 10 s have been reported (Sehlmeyer et al., 2009). The difference in temporal contiguity between CS and US has profound

effects on the development of CRs, as fear acquisition and extinction is more rapid in delay than in trace conditioning in rodents (Beylin et al., 2001; Pavlov, 1927) and humans (Ewald et al., 2014; Knight et al., 2004) but see (Cornelisse et al., 2014).

With respect to the interval between CS and US onset (i.e. lead interval), conditioning in rodents is the strongest in the typical set-up in which the CS is presented alone for a short time before the US is administered, with US presentation overlapping CS presentation in time (Rescorla, 1988). This means that presenting the CS alone for some time (allowing for anticipation of the upcoming US) leads to facilitated fear learning and that it has the ability to measure the CR (cf. Fanselow, 2010). This lead interval needs to be tailored to the CS modality and dependent measurement(s) (see 4.1.1.1, 4.1.2.1, and 4.1.6.1). Other ways of timing the US presentation with respect to the CS result in less strong conditioned responding and are used less frequently, such as *simultaneous* conditioning in which CS and US are presented and terminated at the same time (Gawronski and Mitchell, 2014; Perlmuter et al., 1968), and *backward* conditioning (Andreatta et al., 2013; Barlow, 1956; Mitchell and Lovibond, 2002), which refers to a procedure where the US precedes CS onset (i.e. signalling safety). The general consensus in animal studies is that conditioned responding is decreased by the presence of simultaneous and backward CSs, and consequently, the acquisition of conditioned fear is slowed down. Furthermore, the exact duration of CS and US presentation should be tailored to the outcome measure that is assessed (see 4). Typically, CS duration encompasses several seconds (e.g. 4, 6, or 8s, however, it depends on modality, cf. 2.1.1), especially to allow the development and measurement of physiological responses or to allow participants to give a rating of their subjective state. US duration depends on US modality, which is dependent on how long the stimulus needs to be presented in order to have sufficient unconditioned impact (e.g. in the ms-range for electrical stimulation in comparison to several seconds for emotional pictures, see 2.1.3).

2.2.4. Instructions: fear learning versus fear expression

Careful considerations should be given to if and how participants are instructed about any phase of the fear conditioning procedure, especially regarding the relationship between the CS and US (CS-US contingency).

Instructions provided verbally or in text form before fear acquisition training can either contain no information about the CS-US contingency ('Attend to the visual material on the screen'), can be fully instructed ('Only the blue square will be followed by the aversive stimulus, the yellow square will never be followed by the aversive stimulus'), or anything in between (e.g. 'One of the two pictures presented on the screen will be followed by the aversive stimulus, the other not. You will be able to figure out which one by paying close attention').

Indeed providing some or explicit instructions on CS-US contingency ('instructed fear studies') has distinct advantages, and it may be especially useful when little variance in acquisition learning is desired. This applies to the aspiration of 1) a uniform fear learning and awareness when post-acquisition manipulations or phases are the focus of the investigation, 2) when fear/anxiety expression is the main focus of the investigation, or 3) when the US number has to be limited to reduce US habituation or discomfort due to ethical considerations (especially in vulnerable populations). Indeed, when instructions are compelling enough, a stable level of conditioned responding can be obtained, even across several sessions with only very minimal reinforcement (Klumpers et al., 2010). However, it is important to note that instructed fear or 'threat of US' studies differ with regard to whether the fear expression phase actually contains CS-US pairings (to maintain credibility; Grillon et al., 1993; Mertens et al., 2016; Raes et al., 2014) or not (see Mechias et al., (2010) for a meta-analysis), which has an impact on the strength of the CR (Mertens et al., 2016; Raes et al., 2014).

On the other hand, not providing explicit instructions is advantageous for other specific research questions. Allowing for experience-based associative learning boosts variance in conditioned responding, possibly through increased ambiguity and cognitive demand. More ambiguous experimental situations may be more relevant to the clinical pathology model (Beckers et al., 2013; Lissek et al., 2006) and may often result in a certain percentage of participants that do not acquire or are not able to verbally express CS-US contingencies ('contingency awareness' see 4.2.1). Again, this may represent relevant information, particularly with respect to individual difference variables (see 5).

Importantly however, seemingly subtle differences in whether and how participants are instructed with respect to CS-US contingencies prior to fear conditioning may substantially affect the results and interpretation thereof. First, contingency instructions (but possibly also fear or contingency ratings themselves; see Sjouwerman et al., 2016) do facilitate or even generate contingency awareness, which generally impacts the presence, strength, and development of conditioned fear responses over time (see 4.2.1), and possibly, subsequent experimental phases. More precisely, attention to the (existence of a) relationship between the CS and the US has been shown to be crucial for associative learning (Weidemann et al., 2016). Second, instructed fear paradigms and paradigms that rely on uninstructed, and hence, association-based learning, are likely to rely on (partly) different underlying processes. Again, this is critical, as different processes might be differentially susceptible to specific experimental manipulations (e.g. drugs or individual differences). More precisely, if explicit information about CS-US contingencies are provided, fear responses are typically observed instantaneously, while fear responses evolve over time in uninstructed paradigms (Atlas et al., 2016 although this may not be true for all read-out measures). Authors should be very attentive to these possible differences in the underlying processes between both procedural approaches and explicitly consider this while interpreting results. More precisely, we suggest reserving the term 'fear learning' exclusively for association-based processes that evolve over time in uninstructed paradigms or paradigms with only limited instructions ('If you pay attention, you may be able to predict when the aversive stimulus will be administered'). Hence, whenever possible, 'fear learning' should be clearly discriminated from 'fear expression' in instructed paradigms.

Similar to fear acquisition, extinction can be investigated following provision of instructions ('no US will be delivered') or no instructions with respect to changes in previous CS-US contingency. In contrast to 'instructed fear', instructed extinction has rarely been employed to date, and little is known on the impact of instructed versus uninstructed acquisition on the course of extinction learning. Available data suggest that instructed extinction instantaneously abolishes conditioned responding, which, however, may be restricted to certain outcome measures (see 4) (SCRs: e.g. Hugdahl and Ohman, 1977; Luck and Lipp, 2015; heterogenous findings for FPS Sevenster et al., 2012 and CS types (resistance to instructed extinction in fear-relevant CSs: Hugdahl and Ohman, 1977; Soares and Ohman, 1993 but see Dawson et al., 1986; Rowles et al., 2012) for contradictory findings).

Fear generalization (see 3.3) has also been shown to vary as a function of instructions and participants' beliefs about contingencies (i.e. relevance of specific stimulus features; Ahmed and Lovibond, 2015; Vervliet et al., 2010b). With respect to the impact of CS-US contingency instructions on subsequent experimental phases (i.e. extinction training, extinction recall, or ROF expression), studies are scarce, and the use of heterogeneous methods

(instructed extinction: (Sevenster et al., 2012; instructed acquisition: Mertens et al., 2016) leaves many questions open to future research.

3. Phases of a conditioning protocol

For the different phases of a conditioning protocol, different methodological considerations apply. Many of the methodological decisions on what phases to include, and what these phases entail, will depend on the exact research question. Considerations for the design choices are discussed in the subsections of this chapter for the different phases pre-acquisition (including US calibration and habituation/familiarization), fear acquisition training, fear generalization protocols, extinction training and ROF manipulations.

3.1. Pre-acquisition

In human fear conditioning experiments, two different experimental phases may precede fear acquisition training: a US and/or CS calibration phase and a habituation/familiarization phase. Despite some distinct advantages (see below), it should be noted that pre-exposure to the CSs, the (unpaired) US, or the context might affect the course of subsequent conditioning. Phenomena related to CS and US pre-exposure include latent inhibition of CRs (in humans: Meulders et al., 2012; Vaitl and Lipp, 1997; in rodents: Jordan et al., 2015). In contrast, context pre-exposure seems to lead to a facilitation of context conditioning in rodents (Richardson and Elsayed, 1998) but not in humans (Tröger et al., 2012).

3.1.1. Unconditioned stimulus calibration

The US calibration phase serves the purpose of individually adjusting the subjective aversiveness of the US (mostly electrotactile) to a pre-defined criterion level of aversiveness across participants. This is critical because US aversiveness may impact the salience, which has been shown to affect fear learning and expression (see 2.1.3). In human fear conditioning research, US intensity is commonly set at a level that is perceived '*unpleasant, but not painful*', whereas in pain-related fear conditioning research a '*significantly painful stimulus that demands some effort to tolerate*' is selected. Thereby, many researchers aim for a certain criterion (which is not necessarily communicated to the participants) of self-reported aversiveness using staircase or pain-threshold methods for every participant. The precise procedure differs between laboratories in terms of the endpoints of the applied verbal or visual (Duncan et al., 1989) analog scale (not unpleasant/painful/annoying vs. very unpleasant/painful/annoying) and which criterion is used [e.g. minimum 4 out of 5, (Schmitz and Grillon, 2012), 5 out of 10 (Kircher et al., 2013; Lueken et al., 2014), 7 out of 10 (Haaker et al., 2013), 8 out of 10 (Klumpers et al., 2010)].

To-date, there is no consensus in the field on how to best perform and quantify US calibration for instance in case of electro-tactile stimulation. It is recommended to acquire subjectively rated aversiveness of the selected US prior to and after fear acquisition (and reinstatement) in addition to objective US intensity (e.g., in mA). Furthermore, the number of calibration USs should be limited to a minimally required number per participant to avoid habituation effects.

Importantly, other procedures, such as quantitative sensory testing (Rolke et al., 2006) and quantification of sensory input, are available (Edwards et al., 2005) but these are not widely employed.

Notably, however, studies systematically investigating the impact of US aversiveness on conditioned responding and the acquisition thereof are lacking to date.

3.1.2. Habituation/familiarization

Including a CS habituation or familiarization phase (less common US habituation) during human fear conditioning procedures serves various functions. First, it establishes a baseline response rate, which allows the determination and correction for possible pre-conditioning differences between the to-be-CSs. Second, output systems habituate to an asymptotic level of responding. The latter is especially important for physiological measures that show a steep decline in responding over the first number of trials (orienting responses), which would work against an increasing learning curve for the CS+ to a certain degree. Third, it may be useful to include a brief training phase for rating procedures either during pre-acquisition or during a separate pre-experimental phase, to ensure participants' full understanding of the procedures.

3.2. Fear acquisition training

Fear acquisition training refers to the procedure of CS-US pairing, while the term *fear acquisition* refers to the theoretical process of CR development. Variations in the operationalization of experimental acquisition procedures are manifold, as described in the following sections and in Tables 2 and 3. Fear acquisition is assumed to represent one mechanism how pathological fears can be acquired (Mineka and Oehlberg, 2008; Mineka and Zinbarg, 2006; Ohman and Mineka, 2001). The interested reader is referred to comprehensive reviews for detailed neurobiological underpinnings (for reviews see Maren, 2001; Maren and Quirk, 2004; and rodents: Fendt and Fanselow, 1999).

3.2.1. Differential versus single-cue protocols

The majority of the human studies on fear acquisition employ *differential* protocols in which one stimulus (CS+) is predictive of the US, while a second one is not (CS-; see Fig. 1**A, C**). CRs are quantified by the difference in response amplitude/strength to the CS+ versus the CS-. The differential protocol provides more statistical power as it controls for between-subject differences in general responsivity. Furthermore, a within-subject comparison between stimuli (non)associated with the US is more efficient in terms of resources (no need for a control group; for a discussion of difficulties with appropriate control groups see Prokasy, 1977). Importantly, differential designs are often employed to control for non-associative processes, such as orienting responses and habituation, which is thought to affect both the CS+ and the CS- in a similar way.

Importantly, however, the CS- may not represent a completely neutral control as a differential procedure that does not only involve excitatory conditioning to the CS+ but also inhibitory conditioning to the CS-, which does signal the absence of danger ("safety stimulus"; Lissek et al., 2005a,b). Furthermore, generalization processes (see also 3.3) may occur due to similarities between the CS+ and the CS- (Christianson et al., 2012). The comparison with responding during the ITI may be used to assess the level of generalization to the CS-, but this comparison can be problematic either. Generalization of fear responses can also be induced by the context in which the CS-US association was learned (context conditioning, see 3.2.3), which is the context in which the ITI is also presented (Baas et al., 2008) (cf. Fig. 1**A, C, D**).

Single-cue protocols in turn compare CRs to only one stimulus that is paired with the US (CS) with either a control group (receiving the same number of US presentations but presented randomly or explicitly unpaired with the CS) or the absence of the stimulus (e.g. during the ITI) due to non-existence of a within-subject control condition. The latter however is restricted to outcome measures that allow valid assessment during the ITI, such as heart rate (HR) or probed responses such as FPS (see 4.1.2), and is not available for other commonly employed outcome measures (e.g. SCRs). Single-cue protocols are not very common in human research,

Table 3
A proposal for homogenization and clarification of terminology in fear conditioning research through a clear distinction between procedure, theoretical process, and effect (extending suggestions by De Houwer, 2007; LeDoux, 2014;.

Suggested terminology	Description
Fear[a]	The conscious emotional experience occurring when an organism is threatened (LeDoux, 2014).
Threat	The existence of danger that challenges the well-being of an organism.
Anxiety	The sustained defensive state towards a future-oriented and not stimulus specific threat.
Fear conditioning[a]	The overarching experimental *procedure* including all phases of a conditioning experiment (i.e. fear acquisition training, extinction training, recall test, return of fear (ROF) manipulation, and ROF test).
CR	A response or internal state that is elicited by a CS during (any phase of a) fear conditioning (experiment).
Fear acquisition training	The *procedure* leading to fear learning (i.e. repeated pairing of the CS and the US). On a procedural level, *instructed/experiential* and *uninstructed* fear acquisition training should be discriminated.
Fear acquisition	The *theoretical process* underlying fear learning as the result of fear acquisition training.
Fear learning	Changes in conditioned responding that *result* from fear acquisition training and manifests as *fear expression* as an *indicator* of the underlying theoretical process, i.e. fear acquisition.
Fear expression	The manifestation of conditioned responding at a given moment, mostly during stable phases of responding resulting from acquisition training or in instructed fear paradigms.
Extinction training	The *procedure* leading to fear extinction (i.e. repeated exposure to the CS without reinforcement).
Extinction	The *theoretical process* underlying extinction learning, which is the result of extinction training (i.e. decline in the frequency and/or magnitude of conditioned responding as a consequence of extinction training).
Extinction learning	The decrement in conditioned responding that *results* from extinction training as an *indicator* of the underlying theoretical process, i.e. extinction. In the literature, this has also been referred to as *within-session extinction*[c].
Retention test[b]	A post-extinction test *procedure* that is employed to test for conditioned responding without a ROF manipulation[b] but may take place after the passing of time, and hence, can tap into the spontaneous recovery processes. In the literature, this is often referred to as 'retrieval test' or 'recall test'[c]. Notably, a retention test is procedurally identical to a ROFtest.
Return of fear manipulation	The post-extinction *procedure* (i.e. experimental manipulation) employed to *induce* the re-occurrence of conditioned responding.
Return of fear test[b]	The post-extinction test *procedure* testing for the re-occurrence of conditioned responding following a ROF manipulation. Notably, a ROF test is procedurally identical to a retention test.
Extinction retention[c]	The *theoretical process* underlying the absence of conditioned responding in a retention test. In the literature, this is also referred to as *between-session extinction*.
Return of fear	The *theoretical process* underlying the re-occurrence of conditioned responding in a ROF test or a retention test.
Extinction recall	The absence or decrement of conditioned responding during a retention test at some interval following extinction training.
Return of fear expression	The presence/re-occurrence of conditioned responding during a ROF test at some interval following extinction training.

[a] Based on the absence of the conscious experience of fear (particularly in rodents), it has recently been proposed to rename both the procedure and the process of fear conditioning to *threat conditioning* based on the problem of failure to distinguish between terms referring to conscious experiences and those referring to the processing of stimuli reported in the literature (LeDoux, 2014).
[b] This phase may serve as an additional extinction training phase.
[c] Terminology adapted from (Myers and Davis, 2007).

while majority of the rodent work employs single-cue protocols (cf. Table 1).

3.2.2. Multiple cue protocols

Multiple CSs can be employed to serve as further control stimuli or to investigate ROF processes. For instance, two CS+ and one CS- have been employed during fear acquisition training, whereas only the CS- and one CS+ (CS + E, extinguished) are presented during extinction, but not the second CS+ (CS + U, unextinguished). During the retention test, the CS + E, CS + U, and CS- are presented in the same phase to assess CRs to the CS + E compared to the CS + U (Milad et al., 2007b). Likewise, different CS+ categories are used, and compared to one CS- such as fear-specific versus fear-unspecific CS+ (McNally, 1986; Schweckendiek et al., 2011). In addition to relatively limited procedures with a couple of different stimuli, the use of many different stimuli serving as CS+ and CS- trials was employed recently (Rehbein et al., 2015 used a total of 104 different stimuli).

Employing multiple cue protocols may have the disadvantage that the establishment of contingency awareness (see 4.2.1) and the development of CRs may be delayed or substantially hampered, especially when no explicit instructions are given (see 2.2.4). Furthermore, the used trial number might be problematic in terms of comparability, i.e. balancing all versus each CS+ with CS- trials needs to be critically considered. CRs to each of the multiple cues could also differ from each other during fear acquisition leading to different points of departure for subsequent phases such as extinction and ROF processes.

3.2.3. Context conditioning protocols

In contrast to the typical phasic CRs induced by a discrete cue (i.e. CS) with a limited duration, conditioning to a context induces sustained CRs (see Fig. 1**B and F**). Both modes of conditioning have been proposed to model diverse features of anxiety disorders (Baas et al., 2004; Grillon, 2002a; Grillon et al., 2006a,b) and rely on different neural pathways (Davis et al., 2010).

Context conditioning can occur to any context in which a US is presented, but it has been shown in rodents that it is most prominent when the context is the best predictor of the US (see 2.1.2) (Phillips and LeDoux, 1994). What constitutes a cue and what a context cannot be clearly discriminated, since a context might also be perceived as a combination of different cues represented as one cue (for a discussion on elemental vs. hierarchical representations and neuronal underpinnings, Rudy, 2009). Critical features that

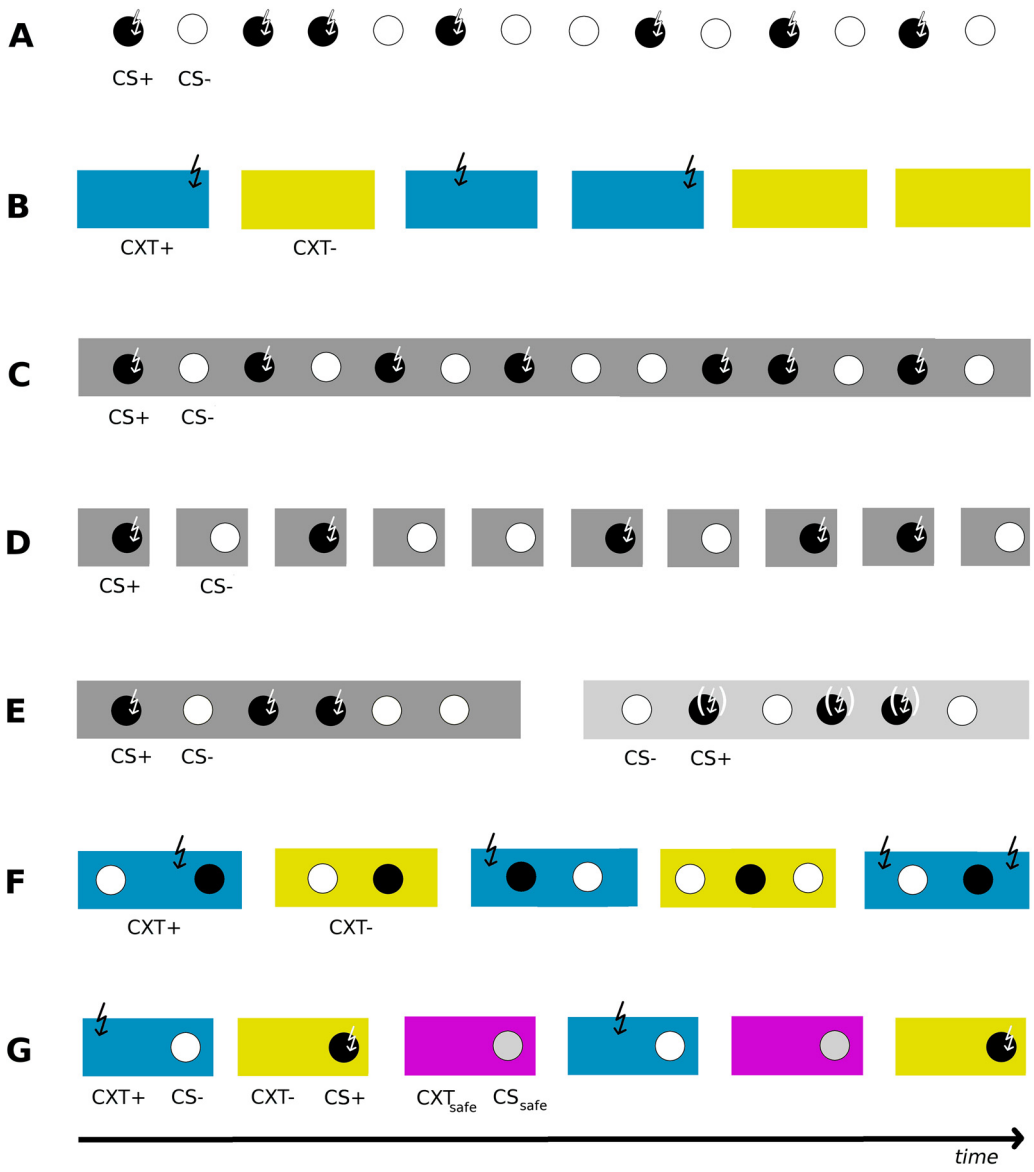


Fig. 1. Examples of cue and context as well as other types of fear conditioning procedures.
A) Cue conditioning without explicit operationalization of a background context. B) Context conditioning. C) Cue conditioning with explicit operationalization of a continuous background context. D) Cue conditioning in a compound cue-context design (i.e., ITI is depicted on a different background context). E) Context-dependent cue conditioning in which the predictability of the CS+ (reinforcement likelihood) depends on the context. F) Cue-independent context conditioning in the presence of non-predictive cues. G) Possbility for design of a combined context-cue conditioning consisting of a predictable condition in which the CS is predictive of the US, an unpredictable condition in which the context is the best US predictor, and a safe condition without US presentation.
Bolt denotes the US.
Contexts highlighted in colors (blue: CXT+, yellow: CXT-, pink: CXTsafe) serve to illustrate contexts of primary relevance to the experimental design whereas contexts highlighted in shades of grey are not or not of primary interest in experimental design.

have been argued for the distinction between responses to CS and context is their respective duration (Walker and Davis, 2008), unidimensional stimulus features versus complex feature compounds (Glenn et al., 2014), or function as an occasion setter signalling when a CS-US relationship holds or not (Balsam and Tomie, 1985; Holland and Bouton, 1999).

Context conditioning is enhanced by manipulations that increase the temporal unpredictability of the US, which may be related to the duration (the longer the situation in which a US may occur, the larger the temporal unpredictability), but which can also be reduced by adding other, more specific predictors of US (i.e. a CS in combined-context-cue paradigms, see 3.2.4) (Fonteyne et al., 2010). Importantly and more specifically, failure to acquire the CS-US contingency (see 4.2.1) in cue conditioning protocols has been shown to promote context conditioning in humans (Grillon, 2002b). More generally, when manipulating context elements within one experimental session, it must be kept in mind that these are all embedded in the general experimental context, and that generally fear-related responses may be potentiated throughout presence in this context (Baas et al., 2002).

One issue that has to be solved when designing a context conditioning experiment is that physiological responses assessed in the US context are in temporal proximity to the USs, while in a neutral context they are not. In cue conditioning, this can be resolved by counterbalancing the conditions that occur directly after a US, but the long context duration with several (or sustained) assessments of physiological state during each context does require alternative solutions (see Baas et al. (2008) for a possible way to resolve this).

3.2.4. Combined context-cue conditioning protocols

While experimental paradigms can be specifically designed to target cue or context conditioning, paradigms for simultaneous assessment of both conditioning types within-subjects (see Fig. 1**E, F, and G**) have been developed (Alvarez et al., 2011; Baas et al., 2004, 2008; Fonteyne et al., 2009, 2010; Grillon et al., 2006a; Lonsdorf et al., 2015a, 2014; Marschner et al., 2008). These combined context-cue conditioning protocols allow for an investigation and within-subject comparison of phasic and sustained responses modelling cue and context related learning processes respectively (Baas et al., 2004; Grillon, 2002a; Grillon et al., 2006a). They represent an ecologically valid approach when studying fear learning, as in natural environments danger may sometimes be associated with specific cues, but oftentimes with a more general environment. Cue and context conditioning have been implemented by the presentation of an experimental context (see 2.1.2) with embedded presentations of one or more discrete cues (CSs, see Fig. 1**E–G**). For instance, virtual reality rooms (i.e. contexts) have been combined with flash bulbs (i.e. cue) of a distinct colour (Grillon et al., 2006a). A distinction can be made between manipulations in which the US is always presented together with a cue (i.e. CS), making the CS a more specific predictor of the US (see Fig. 1**E**), versus an unpredictable condition, in which the US is presented mostly in absence of the CS, and hence, cannot be predicted by the cue (see Fig. 1**F**). Both conditions can ideally be compared to a neutral or safe condition (no US presented) allowing for analogous comparisons as in differential cue conditioning with a safe control stimulus (i.e. CS-). This is particularly important as studies differ with respect to the exact implementation of unpredictability (i.e. US presentations during the cue in the unpredictable condition or not). An influential instructed threat experiment with different contexts in which the US is either presented in the presence of a visual cue (predictable) or in its absence (unpredictable) has shown that contextual anxiety is especially strong in the unpredictable condition (Schmitz and Grillon, 2012) (see Fig. 1**G**).

Despite some advantages, combined context-cue paradigms require cautious analysis strategies. Inherent differences in the nature of responses to contextual and cued stimuli put constraints on comparability between phasic and sustained CRs on an (unprobed) autonomic (SCR vs. SCL; see 4.1.1.2) and neural level (stick functions vs. box car regressors; see 4.1.6.2). Hence, probed outcome measures such as FPS (see 4.1.2) might overcome this limitation (Schmitz and Grillon, 2012).

For FPS, Schmitz and Grillon (2012) suggest the quantifications of 'fear potentiated' (difference in responding to cue and context within the predictable condition) and 'anxiety-potentiated' startle (difference in responding to the context in the unpredictable vs. safe condition). This is based on the observation in most cue-context conditioning paradigms with relatively long context durations (in the order of 1–3 min, typically manipulated with virtual environments) that potentiation of startle is apparent throughout the duration of the threat context (Baas et al., 2008; Grillon et al., 2006a). Hence, it is generally assumed that the potentiation of startle to cues presented within this context is additive on top of the sustained context potentiation. Others have however implemented different analysis strategies (comparison of the predictable cue and unpredictable context with their respective safe counterparts) (Haaker et al., 2013; Lonsdorf et al., 2015a, 2014). Neither of these strategies may be completely satisfactory; the first is based on the assumption of additivity, and the latter method of quantifying cue potentiation may be confounded by the effects of context potentiation regarding startle potentiation likely extending to other outcome measures.

It is important to note that the response enhancement is not restricted to the best US predictor in a given experimental condition (i.e. unpredictable context and predictable cue). More specifically, responses to the context in which a cue predicts the US are potentiated against the safe context and similarly responses to the cued CS are also enhanced in the context in which the US is presented unpaired with this CS (Haaker et al., 2013; Lonsdorf et al., 2015a, 2014). This is especially the case when CS-US contingency is not obvious and learned only over time, causing participants to first associate the US with the context (Baas, 2013).

3.3. Fear generalization protocols

Fear generalization describes the transfer of fear conditioned responding to a specific stimulus to stimuli resembling the original CS+ (Dunsmoor and Paz, 2015; Honig and Urcuioli, 1981; Lissek et al., 2008a). Thereby, fear generalization generally serves adaptive functions that allow appropriate defensive responses to novel stimuli based on previous experience with similar cues (i.e. 'better safe than sorry' when cues resemble threat cues). However, when non-threatening stimuli are inappropriately perceived as harmful, fear generalization can become maladaptive and constraining (Lissek et al., 2008a).

Following the observation that patients with anxiety disorders tend to generalize fearful responding from the CS+ to the CS- (Duits et al., 2015; Lissek et al., 2005a,b), specific protocols assessing the extent of this generalization ('generalization gradients') to similar cues were developed (see Table 2). For example, two highly discriminable stimuli (i.e. small and large annuli) serve as CS+ and CS- during fear acquisition training (Lissek et al., 2008a). In a subsequent generalization test phase, the generalization of fearful conditioned responding to intermediately sized annuli is investigated as the slopes of generalization gradients. Extending the work of Lissek, more refined paradigms have been developed (Dunsmoor et al., 2009; Onat and Büchel, 2015) also for contextual generalization (Andreatta et al., 2015) or the influence of conceptual knowledge using unique exemplars of superordinate object categories (e.g. animals or tools) as CSs (Dunsmoor et al., 2012).

As fear generalization in humans has recently been comprehensively reviewed (theoretical accounts of higher-level cognition such as concpetual knowledge: Dunsmoor and Murphy, 2015; Dunsmoor and Paz, 2015; individual diffrences and implications for anxiety disorders: Dymond et al. (2015), we refer the interested reader to this work.

3.4. Extinction training

Extinction training represents the procedure of unreinforced CS presentation, after which the CS elicits reduced or no CRs anymore, a process referred to as extinction (cf. Table 1). Extinction learning can take place as soon as the first unreinforced CS+ trial is presented. It is assumed to represent one mechanism behind various components of cognitive behaviour therapy (e.g. exposure therapy), which aims to reduce (learned) fears (for reviews see Dunsmoor et al., 2015; Milad and Quirk, 2012; Vervliet et al., 2013c). Mechanistically, extinction training is thought to create a new 'safety' memory that inhibits, but typically, does not erase the original fear memory (for theoretical considerations see Bouton, 2004; Bouton, 2014; Delamater, 2004, for cellular and molecular pathways mediating extinction learning which have mainly been studied in animal research see Fitzgerald et al., 2014; Herry et al., 2010; Milad and Quirk, 2012; Myers and Davis, 2002; Myers and Davis, 2007; Tovote et al., 2015). However, interfering with the reconsolidation process (i.e., rendering the molecular memory trace in the brain plastic upon recall and thereby allowing to modify it and ultimately consolidate a modified memory) comprises one possibility to erase the original fear memory (see Agren, 2014; Fernández et al., 2016;

Meir Drexler and Wolf, 2016 for reviews including methodological discussions).

Similar to the many different conditioning protocols existing for fear acquisition, there are multiple ways to extinguish CRs, including direct and vicarious extinction training as well as instructed extinction protocols which will not be discussed in detail here (vicarious extinction: Golkar et al., 2013b; observational fear learning: Olsson and Phelps, 2007). Several procedures for extinction protocols (i.e., immediate extinction versus delayed extinction training, extinction training with multiple contexts or cues, gradual extinction training) will be discussed in the following Sections (3.4.1–3.4.3).

3.4.1. Immediate versus delayed extinction training

In the vast majority of recent studies of fear extinction in humans, extinction training follows immediately after acquisition training, without any pause (see Table 2; except for possibly providing ratings, see 4.2.1), and generally any other changes to signal the transition (e.g. instructions). Yet, over the past decade, it has become apparent from rodent and human work that the delay between fear acquisition and extinction training influences both the time-course as well as end-point extinction performance (for a review based primarily on rodent work, see Maren, 2014). Initially, it had been suggested that extinction training initiated shortly after fear acquisition training (*immediate extinction*) promotes resistance to ROF. In turn, extinction training taking place after allowing for fear memory consolidation (e.g. 24 h; *delayed extinction*) was argued to preferentially induce (more labile) inhibitory learning (Myers et al., 2006).

Recently (for a review see Maren (2014), however, immediate extinction training has been shown to be less or equally effective compared to delayed extinction training in suppressing fear as evidenced in both rodents and humans (Archbold et al., 2010; Chang and Maren, 2009; Huff et al., 2009; Merz et al., 2016), but contradictory findings have been published (Golkar and Öhman, 2012; Myers et al., 2006; Norrholm et al., 2008). This phenomenon has become known as the '*immediate extinction deficit*' (e.g. Chang and Maren, 2009; Maren, 2014). Boundary conditions contributing to this phenomenon have not yet been comprehensively delineated, but it should be noted that short (i.e. 48 h) versus long (i.e. 7 days) extinction-to-test delays have been shown to produce opposite results in rats (Johnson et al., 2010). While the short extinction-to-test delay led to higher fear recall in the immediate extinction group, the long extinction-to-test delay provoked higher fear recall in the delayed extinction group. Hence, this topic still needs more attention in future experiments.

In addition to long-term reduction of fear, the *time-course of within-session extinction* (see Tables 1 and 3) is also affected by acquisition-to-extinction timing, whereby immediate extinction is characterized by slower and incomplete extinction learning as evidenced by rodent (Archbold et al., 2010; Chang and Maren, 2009) and human work (Golkar and Öhman, 2012; Kim et al., 2010; Norrholm et al., 2008).

Allowing for fear memory consolidation before extinction training (i.e. longer acquisition-to-extinction delay) is ecologically more valid for most situations, and would be clinically as well as theoretically relevant. Yet, most human work is based on protocols employing immediate extinction training. Rodent work in turn mostly employs delayed protocols (see Table 1) resulting in a translational gap between species. Hence, the employment of delayed extinction protocols in future studies is recommended.

Nevertheless, some research questions warrant immediate extinction designs, such as studying the effect of immediate treatment after trauma or the effect of interrupting consolidation of the original fear memory by extinction training. When immediate extinction protocols are used, attention should paid to subtle signals possibly marking the onset of this new experimental phase with changed CS-US contingencies through explicit breaks of the experimental flow [e.g. context changes (see 3.5.2) or ratings (see 4.2.1)]. This transition from the acquisition phase to the extinction phase is not well studied to date, but recent work suggests that a context change from acquisition training to extinction training induces CS+ related response enhancement during early extinction training but seems to facilitate extinction learning (Sjouwerman et al., 2015), which calls for a careful consideration of these issues in the conditioning protocol.

The first trials of immediate or delayed extinction can also be referred to as 'fear recall' (cf. Table 2; in particular in delayed protocols), when participants are not informed with respect to the beginning of the extinction phase and the omission of the US (especially after acquisition training with a partial reinforcement rate). The number of extinction trials considered to test for fear recall differs between labs ranging from the first trial for each CS to several trials. Due to (re-)extinction processes beginning relatively fast, it seems unreasonable to use more than five trials per CS to test for fear recall, although the total amount of extinction trials and the specific outcome measure need to be considered Fig. 2.

3.4.2. Extinction training employing multiple contexts or cues

As opposed to the classical extinction procedure (usually conducted in a single context), extinction procedures conducted in several novel contexts have been shown to be particularly effective at reducing the ROF expression (i.e. renewal) in rodents (Chelonis et al., 1999; Denniston et al., 2003; Gunther et al., 1998; Laborda and Miller, 2013; Thomas et al., 2009) and healthy humans (Balooch et al., 2012; Dunsmoor et al., 2014; Glautier et al., 2013), as well as in clinical and pre-clinical samples (Shiban et al., 2013; Vansteenwegen et al., 2007; Vervliet et al., 2007). Notably, however, also null-findings have been reported in humans (MacKillop and Lisman, 2008; Neumann et al., 2007), possibly due to the absence of long-term effects despite short-term beneficial outcomes (Shiban et al., 2013).

In addition, an extinction procedure might also include multiple cues in order to reduce ROF, which has not been implemented in human fear conditioning research so far. However, the clinical approach yielded first insights into the beneficial effects: exposure to four spiders (compared to one) led to an absent increase of fear at a 3-week follow-up assessment in spider-fearful individuals (Rowe and Craske, 1998). Likewise, an approach combining multiple cues and multiple contexts during exposure has recently been used in spider phobics (Shiban et al., 2015a): indeed, multiple stimuli led to beneficial effects compared to a single stimulus in the long run. Exposure in multiple contexts reduced ROF in the short run, but increased ROF in the long run (20 days later). Critically, the combination of multiple cues and multiple contexts was not superior compared to the different approaches alone.

Methodological considerations related to multiple context/cue manipulation include questions of randomization (e.g. presentation of context/cue blocks or full randomization) as well as, most importantly, the selection of an appropriate context/cue for the critical ROF test. More precisely, one of the extinction contexts/cues, the acquisition context/cues or a novel context/cue may be selected, which is likely to impact on retention performance, as these subtle differences in procedure tap into different underlying processes.

3.4.3. Gradual extinction training

There are two approaches to reduce CRs during extinction training, either by an abrupt omission of presenting the US (i.e. change in CS-US contingencies), which has traditionally been done, and is referred to as *extinction learning*. Alternatively, gradually reducing the intensity of the US or its frequency results in *US re-evaluation,* which has also been referred to as *gradual extinction training*. Grad-

ual as compared to traditional extinction has recently been shown to be more efficient in preventing spontaneous recovery and ROF expression assessed by freezing behaviour in rodents (Gershman et al., 2013) and humans (Shiban et al., 2015b), even though the beneficial outcome was restricted to FPS as an outcome measure in humans. As gradual extinction training has only recently been introduced, procedures for gradual US intensity reductions need to be validated methodologically in the future.

3.5. Return of fear manipulations

Different phenomena of reoccurring CRs (i.e. ROF) after successful extinction learning have been observed in both rodents and humans, including spontaneous recovery, renewal, reinstatement and rapid reacquisition (Bouton, 2002; for a recent review in humans see Vervliet et al., 2013c). Procedures that induce ROF in the laboratory serve as experimental models for clinical relapse, which affects a substantial percentage of patients (Craske, 1998). Notably, however, in experimental work, proxies of ROF are studied rather than full blown fear responses.

In laboratory experiments, when testing for retention of fear following acquisition and extinction training, the response that is measured depends on which of the two opposing and co-existing memory traces (original fear memory vs. extinction memory; see 1) is dominant. When the CR is low or absent during testing, this is interpreted as dominance of the extinction memory trace, labelled as *extinction recall*. Conversely, when the CR is strong, dominance of the fear memory trace is assumed, which is referred to as *ROF expression* or *fear recall*.

Hence, it is noteworthy that the terminology (cf. Table 3) used for what is observed during the retention test is often employed in a way that depends on the exact research question and direction of the hypothesis. For instance, an expected increase in CRs during a test session might be interpreted as ROF expression or (high) fear recall or the absence of/deficits in extinction recall. Future research should pay special attention to the terminology with clearly distinction between procedures and processes (see Table 3).

3.5.1. Spontaneous recovery and extinction recall protocols

Spontaneous recovery refers to the return of CRs as a function of time after successful extinction learning. Notably, extinction retention refers to the absence of CRs at a later test time point, which is interpreted as the successful expression of extinction memory. Most notably, the protocols for tests of spontaneous recovery and extinction recall in humans are completely identical (see Table 2), as both are tested at a single time-point following extinction training (typically with a minimum of 24 h later) without any active experimental manipulation to probe reactivity [as opposed to renewal (see 3.5.2) and reinstatement (see 3.5.3)]. Hence, in the existing literature, extinction retention and spontaneous recovery can only be distinguished conceptually, as they represent two opposing extremes with respect to the (expected) outcome of the dominance of the extinction over the fear memory trace, and vice versa. Importantly, however, as spontaneous recovery should be proportional to the length of the extinction training-test time interval (see Quirk (2002) for rodent work), multiple test time points need to be considered in future studies for the spontaneous recovery to map the responding as a function of time. Having only one time point included as test for ROF, we recommend not using the term spontaneous recovery, but rather using the term retention test. This neutral term does neither refer to the direction of the hypothesis (i.e. ROF or extinction retention) nor to the development of CRs over time (which should be actually shown for spontaneous recovery).

In human studies, the time interval between extinction training and extinction recall/spontaneous recovery tests varied between 24 and 94 h across studies (for a summary see Vervliet et al., 2013c), but systematic investigations on the extinction training-to-test interval are still awaited.

3.5.2. Renewal protocols

The renewal effect describes ROF expression induced by a contextual change between extinction training and the subsequent ROF test (see Table 2). For instance, in so-called ABA renewal procedures, it has been shown that a conditioned fear response, which is acquired in Context A, and extinguished in Context B, returns in the original context (A) (Bouton and Bolles, 1979; Vervliet et al., 2013a). Yet, renewal can also be triggered by a mere switch from the extinction context to a new context, as in ABC renewal (where fear returns in the new context C; Bouton and Bolles, 1979; Hermann et al., 2016, and in AAB renewal (as fear that was acquired and extinguished in the same context returns in the new context B; Bouton and Ricker, 1994). Control conditions for renewal are typically AAA (all learning phases at the same context) for AAB and ABA renewal, or ABB for ABC renewal (Bouton, 2014; Vervliet et al., 2013a). For a comprehensive review of renewal, clinical implications, and methodological considerations in humans, refer to (Vervliet et al., 2013a).

3.5.3. Reinstatement protocols

The reinstatement effect describes ROF expression following (unannounced) re-exposure to the original US (human work: Bouton and Bolles, 1979; Haaker et al., 2013; rodent work: Rescorla and Heth, 1975) or a different US (human work: Sokol and Lovibond, 2012; rodent work: Rescorla and Heth, 1975) after successful extinction learning. The context plays a pivotal role in CS-discrimination and quantity of the ROF following reinstatement in rodents and humans, and consequently, also in theories on the reinstatement phenomenon (for a review see Haaker et al., 2014). Human reinstatement studies, their clinical implications, context-dependency, as well as methodological (design, data analysis) considerations and individual difference factors have been thoroughly discussed in a recent review (Haaker et al., 2014).

3.5.4. Rapid reacquisition

A fourth demonstration of ROF is rapid reacquisition after extinction, which has been mainly demonstrated in non-human animals (Napier et al., 1992; Ricker and Bouton, 1996). In this case, introducing CS-US pairings after extinction can result in more rapid reacquisition of the original CS-US contingency than acquisition with a novel CS. One explanation for this effect is that the first CS-US presentation during reacquisition resets the acquisition context and thereby re-activates the CS-US memory trace, which is not erased during extinction training (Bouton, 2002; but see McConnell and Miller (2014) for an overview of alternative explanations). Human studies demonstrating rapid reacquisition are however scarce, although re-acquisition has been reported to be compromised in groups with disrupted reconsolidation (Agren et al., 2012; Soeter and Kindt, 2011b).

3.5.5. General design and analysis considerations for return of fear manipulations

Several considerations with respect to design and analysis strategies are important in studies investigating ROF phenomena, which have been summarized in recent reviews (for reinstatement: Haaker et al., 2014; for renewal: Vervliet et al., 2013a).

In brief, the most important recommendations comprise first, the inclusion of a brief (re-)extinction phase prior to the context switch (renewal) or in the unpaired US presentations (reinstatement), in particular, in multiple day experiments (see 4.3.2). This approach provides information about extinction retention by analysing the first trials and additionally establishes a baseline of

responding (i.e. last couple of trials) for comparison of responding during the test within-subject. Not including this phase results in the inability to unequivocally attribute the results to spontaneous recovery or other ROF manipulations. Second and relatedly, adequate statistical comparisons (i.e. statistical comparison to a pre-return of fear manipulation phase) need to be considered carefully. Thereby, a critical issue in ROF research is the transience of the returning fear response that often only manifests in a limited number of single trials (for a systematic investigation in reinstatement see Scharfenort and Lonsdorf, 2016). Third, appropriate control conditions or groups (e.g. no context switch or no reinstatement US presentation) for the respective research question should be selected. Fourth, the subsequent testing of spontaneous recovery, renewal, and reinstatement in the same experimental phase, which is only separated by a number of re-extinction trials, has been employed previously (e.g., Milad et al., 2005). While this procedure generates potentially informative insights, the major disadvantage of the confounding effects of the preceding experimental ROF manipulation on the subsequent test need to be evaluated empirically before this procedure can be recommended. To date, the interpretation of data generated by these designs is limited by a lack of knowledge on the specificity of such findings and potential interference of different manipulations. Until it has been established that the order of manipulations has no effect, choosing one ROF manipulation to follow a spontaneous recovery/extinction retention test is highly recommended.

4. Outcome measures in fear conditioning research

Generally, human emotions can be studied on different response levels: (1) verbal reports about subjective experiences, (2) behavioural expression, and (3) physiological as well as (4) neurobiological changes (e.g. Bradley and Lang, 2000), which however do not necessarily converge (see 4.3.1 for a discussion on considerations). Thereby, the choice of outcome measure should be guided by and tailored to the process under study and the action disposition that is primed, that is whether active avoidance is possible or not (e.g. in human and rodent work: Fanselow and Poulos, 2005; in rodent work: Lang et al., 2000).

For ethical and methodological reasons, the CRs acquired in human fear conditioning are rarely strong enough to elicit a behavioural response such as flight (Löw et al., 2015), explaining to some degree why behavioural indices have rarely been employed until now (Beckers et al., 2013). Hence, the following chapters focus on subjective as well as physiological and neurobiological outcome measures.

4.1. Physiological and neurobiological outcome measures

Psychophysiological indices are commonly applied and have the distinct advantage of not being subject to self-report biases and providing a link to animal research. The most commonly used physiological indices of human fear responding are skin conductance responses (SCRs) and the FPS reflex. HR and pupillary response are however employed less frequently. Therefore, the former will be discussed in detail in the following sections, whereas the latter will be discussed more briefly. Fig. 2 illustrates prototypical reactions for the above mentioned measures in fear conditioning. Furthermore, neurobiological methods employed in fear conditioning research, such as electroencephalography (EEG), magnetoencephalography (MEG) and fMRI will be briefly discussed with a focus on fMRI.

Importantly, providing general methodological guidelines is beyond the scope of this work and we refer the interested reader to focused general guidelines papers (startle: Berg and Balaban, 1999; startle: Blumenthal et al., 2005; SCR: Boucsein et al., 2012; HR: Jennings et al., 1981; fMRI: Poldrack et al., 2016, 2008) for recommendations with respect to equipment, electrode placement, data recording, response quantification, and data post-processing. Here, we will only briefly summarize the most important methodological considerations specifically tailored to fear conditioning research.

Thereby, we will particularly highlight the design and analysis choices when clear recommendations for fear conditioning research are absent. We hope that this may set the ground for a common groundwork and foster discussions about this topic, and ultimately aid finding a consensus for the field.

4.1.1. Electrodermal activity

The first (Steckle, 1933; Switzler, 1934) and still most widely employed index of conditioned fear responses is the electrodermal activity (EDA). (see Boucsein et al., 2012; Dawson et al., 2007 for reviews on the anatomical and physiological bases and recommendations on data recording).

Importantly, EDA may be measured as SCR or as *skin conductance level* (SCL). Thereby, SCR refers to a phasic response to a stimulus, that is, the difference between a pre-stimulus and the peak post-stimulus skin conductance (Lykken and Venables, 1971). SCL in turn refers to the average SCL exclusive of phasic activity during a specified time period (cf. Lykken and Venables, 1971). In fear conditioning research, SCR is commonly applied in cue conditioning paradigms where the CS+ onset typically elicits a stronger SCR (i.e. larger amplitude) as compared to the CS-. The application of SCL in turn is mainly applied in context conditioning (see 2.1.2) where a larger SCL is observed for the threat-associated context (CTX+) than for the safety-associated context (CTX-). The use of the frequency of non-specific SCRs (non.SCRs, see Boucsein et al., 2012) in fear conditioning research has mainly been employed in the 1980ies and 90ies (Lovibond, 1992; Murrin and Kimmel, 1986; Vaitl et al., 1985) and will hence not be discussed in detail here.

Note, that the term Galvanic skin response (GSR) has often been employed interchangeably with SCRs. In a narrower sense, GSR however refers to phasic changes generally, while SCR refers to elicited phasic changes in skin conductance (Lykken and Venables, 1971).

4.1.1.1. Paradigm considerations. As phasic SCRs are elicited by salient or novel stimuli in general, other experimental stimuli than the CS and the US commonly elicit SCRs (e.g. startle probe, ratings, and unexpected events). Hence, including time-stamps of these additional stimuli of no interest in the recording software is most helpful. On the other hand, (non-spontaneous) SCRs cannot be assessed during unstimulated experimental phases (e.g. ITI, long stimulus presentations). SCL in turn can be measured continuously but as phasic SCRs impact SCL, care should be taken to assure an equal number of potentially SCR eliciting events (e.g. startle probes, ratings) during all experimental conditions (e.g. contexts) during which SCL is assessed.

SCRs are slow responses that typically have an onset 1–4 s post stimulus and reach their peak 0.5–5 s later (see also 4.1.1.2). Consequently, experimental timing needs to allow for adequate temporal spacing (i.e. minimum 6 s optimally longer is recommended) between different experimental stimuli (ISI, ITI; 2.1.4) to allow a return to baseline. A fast sequence of stimuli inevitably leads to superimposed SCRs which suffer from distorted amplitudes and temporal characteristics (Boucsein et al., 2012; Dawson et al., 2007) even though certain analysis methods might be able to correct for this (4.1.1.2).

Furthermore, the amplitude of SCRs decrement with repeated presentations of the same stimuli (i.e., habituation; Boucsein et al., 2012; Dawson et al., 2007) which puts constraints on the possible length of an experiment as well as on across-days comparisons in

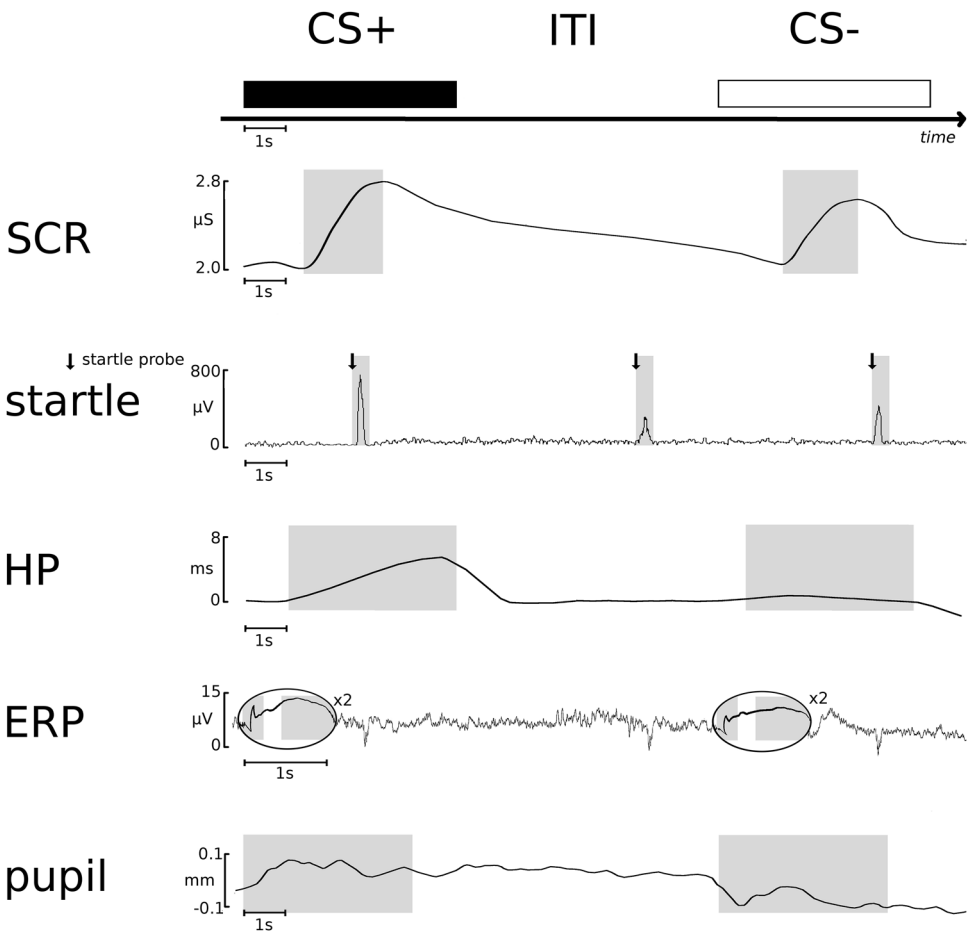


Fig. 2. Prototypical yet exemplary psychophysiological responses in a differential cue conditioning paradigm with visual CS of 5 s duration and electro-tactile US occurring 250 ms prior to CS+ offset. The selected time course illustrates two consecutive trials towards the end of acquisition training with a partial reinforcement rate, during which the presented CS+ trial is not reinforced (i.e. US and UR are not shown).
Sensitive time windows are shaded in grey. They highly depend on the nature of the dependent variable and may overlap within a modality or interfere between modalities. Note that sensitive time windows do not necessarily overlap in time for different dependent measures.SCR shows raw skin conductance changes (Dawson et al., 2007). Fear-potentiated startle is exemplarily illustrated as induced by an auditory startle probe (95dB white noise burst, indicated by an arrow) during CS+ and CS- presentation, as well as during the inter-trial interval (ITI; rectified single subject data derived from Sjouwerman et al., 2015). Heart period (HP) describes changes in interbeat intervals, with longer intervals being a deceleration in heart rate, and data and data on event-related potentials (ERP; 200% magnification) depicts changes in voltage at the Pz-mastoid (both adapted with permission from Panitz et al., 2015). Pupil response shows continuous pupil reactivity under the assumption of isoluminant stimulation (Reinhard and Lachnit, 2002)

multiple day experiments (see 4.3.2). In addition, extinction success as measured by SCRs may both result from genuine extinction learning or from simple habituation processes.

4.1.1.2. Response quantification. For SCRs, a range of methods is available for the response quantification, such as scoring of trough-to-peak (TTP) responses, scoring the 'area under the curve', decomposition, or General Linear Model (GLM) – based deconvolution methods.

Most commonly, the TTP method is applied whereby a maximum value ('peak') is subtracted from a lower preceding value ('foot' or 'trough') in a given time window. Generally, a response window of 1–4 s post-stimulus onset is used to determine the onset of the reaction and a latency from a trough to peak of 0.5 s to 5 s with a minimum response amplitude between 0.01 µS and 0.05 µS is recommended (see Boucsein et al., 2012; Fowles et al., 1981). TTP values can however differ because different strategies employ different definitions of the trough (e.g. average baseline before stimulus onset or a minimum value at response onset). As no reproducible 'basal' level of conductance exists at rest, a minimum value at response onset has been recommended (Lykken and Venables, 1971; Prokasy, 1974). Notably, the minimum possible SCR is always zero (Lykken and Venables, 1971) and hence it cannot take negative values. However, different response quantification approaches can result in negative values, for instance, when a phasic SCR is absent while decreasing skin conductance is observed in a given time window (including baseline-corrections). The integration of such negative values is however difficult as they are physiologically not plausible.

Furthermore, time windows for the definition of SCR onset have been subject to discussion. For CSs a sub-division into a first interval response and a second interval response (FIR vs. SIR; Prokasy and Ebel, 1967) has been suggested, though both show a high correlation (Pineles et al., 2009a).

TTP scoring is often employed manually or semi-manually (i.e. computer-assisted) but open-source tools offering a graphical user interface are available (e.g. ANSLAB, http://www.anslab.net/doku.php; Blechert et al., 2016; Autonomate; https://web.duke.edu/mind/level2/faculty/labar/autonomate.html; Green et al., 2014).

Other methods rely on a decomposition (Ledalab; www.ledalab.de; Benedek and Kaernbach, 2010) or a GLM-based deconvolution approach (PsPM or formerly SCRalyze; http://pspm.sourceforge.net/; Bach et al., 2013). The former attempts the separation of the tonic (i.e. SCL) and phasic (i.e. SCR) activity by estimating a

driver function. The suggested response measure thereby represents the average of all above-threshold SCRs in the pre-defined response window after subtracting the tonic activity. The latter, in turn, employs a canonical SCR function (Bach et al., 2010) yielding a parameter estimate for each experimental condition. It is important to note that both approaches make the claim to be able to deal with ITI/ISIs as short as 2 s (Bach et al., 2010; Benedek and Kaernbach, 2010), which represent a major problem for common TTP approaches due to overlapping responses (Boucsein et al., 2012; Dawson et al., 2007).

Irrespective of the software and approach employed for response quantification, it is highly important to quantify both CRs and URs. In particular, for studies relying on group comparisons (see 5.3), it is crucial to demonstrate the absence of differences in unconditioned responding. Furthermore, URs may help to identify physiological non-responders (see 4.3.6 for definition and treatment of non-responders) and for range-correction of data (see 4.1.1.3). It is important to note that many researchers have observed (e.g., Tabbert et al., 2005) that latency of URs in SCRs may be shorter than the latency for CS-related SCRs. Hence, URs may have a response onset <1 s and scoring criteria have been adjusted accordingly by some authors (Tabbert et al., 2005).

4.1.1.3. Transformations and corrections. The distribution of SCR data is regularly skewed, mainly due to non-responses (i.e. 'zero-responses'; see 4.3.6), which occur more often in CS- trials than in CS+ trials, and more often during extinction than during acquisition training. Differences in skewness between conditions can pose a problem to parametric and non-parametric tests alike and hence logarithmic or square-root transformations, which can compensate for skewed distributions (Levine and Dunlap, 1982), are frequently employed prior to statistical analyses.

In addition, averaging across several trials can further compensate for a skewed distribution in single trials. In any case, the success of such corrections should always be tested before analysis. Importantly, for a meaningful test of a main effect of CS type in an analysis of variance, only the within-subject means for the CS types have to be normally distributed (as only these are tested). If the normal distribution is violated for single trials or averages across few trials, this only affects the main effect of trial and its interactions.

In addition, a range-correction is often applied to correct for inter-individual variance (recommended by: Lykken, 1972; Lykken and Venables, 1971). However, such a procedure may be problematic for between-subject comparisons (Ben-Shakhar, 1985) if groups differ with respect to their range or maximum SCR (e.g. SCRs to the US) and as differences in maximal responding between groups might be neglected. In particular, in fear conditioning research, studies differ in the definition of maximum SCR, which can be based on CRs only, URs only, or both ('researcher's degree of freedom').

Similarly, decisions on whether to employ a single maximum SCR value across all sessions or experimental days (see 4.3.2) or a separate one for each session/day may affect results. An alternative to account for inter-individual variance represents the z- or T-transformation of each raw SCR (Boucsein et al., 2012). To allow for replicability of results, procedures must hence be precisely stated (see Table 4).

4.1.2. Fear-potentiated startle

The startle response is a defensive sequence of reflexes elicited by a suddenly occurring sensory event (Landis et al., 1939). In humans, the most reliable and fastest component of the startle reflex sequence is the startle eyeblink response (Blumenthal et al., 2005; Blumenthal, 2015; Lang et al., 1990), as measured with electromyography (EMG) at the orbicularis oculi muscle (which closes the eyelid during a blink).

The term FPS refers to the finding that the startle reflex elicited by a sudden stimulus is increased in the presence of a threatening as compared to a non-threatening stimulus (in rodents: Davis and Astrachan, 1978). The neural pathway of the startle reflex as well as its affective modulation has been extensively delineated in rodents (e.g., Davis and Whalen, 2001; Koch, 1999). Its high translational value (Fendt and Koch, 2013) and sensitivity to individual differences, clinical diagnoses, and task demands (Grillon and Baas, 2003) renders the startle reflex a particularly useful tool in research on fear and anxiety. In humans however, startle recordings have been restricted to the behavioural laboratory until simultaneous EMG-fMRI measurements have recently become technically feasible (Lindner et al., 2015; van Well et al., 2012).

4.1.2.1. Paradigm considerations. The startle reflex is a probed response which is typically elicited by the so-called startle probe, a brief burst of white noise (typically 50 ms 95–105 dB) with an instantaneous rise-time usually presented binaurally via headphones or can be elicited through the presentation of an airpuff (Lissek et al., 2005a,b). Generally, physical properties of the auditory startle probe, such as intensity, rise time, and bandwidth, but also attention to the probe as well as background conditions (luminescence; i.e. dark-enhanced startle) are known to affect both startle amplitude and startle probability (Blumenthal (2015); i.e. the liklihood of the startle reflex to occur; Blumenthal and Berg, 1986). In addition, a startle habituation phase (i.e. the presentation of 2–10 startle probes) prior to the experiment is crucial to separate initial reactivity from task-related responses (Blumenthal et al., 2005; Blumenthal, 2015) (see 3.1.2).

As the startle reflex is probed, it can be evoked, in principle, at any time-point (but see Weike et al., 2008) during CS presentation, but also during the absence of a CS (e.g. during the ITI or a context presentation). Hence, in contrast to SCRs, FPS allows for a comparison not only between CS+ and CS-, but also of both CS with a baseline condition (e.g. ITI, context). This is highly relevant for between-group comparisons with differing baseline anxiety levels but also when the valence of the background context changes throughout the experiment (Grillon, 2002a) and can be useful to compare unspecific context effects after a manipulation of time or ROF induction (see 3.5).

Many design aspects are to be considered when including FPS as an outcome measure (for a detailed general discussion see Blumenthal et al., 2005), even though most of the widely accepted aspects have not been systematically studied. This includes probing or not probing every trial, jittering probe-US intervals as well as CS-probe intervals (to avoid predictability), as well as directed attention to the startle probe (Panayiotou et al., 2011). Furthermore, special considerations are required when combining FPS and SCR measures, as described in paragraph 4.3.1.

Finally, the startling auditory probe used to elicit the blink reflex may also impact on ongoing processes (Blumenthal, 2015), which has been recently shown experimentally (Sjouwerman et al., 2016) in the first study that directly originated from methodological discussions within the EIFEL-ROF network. Importantly, this calls for caution when directly comparing studies that do or do not include startle probe presentations.

4.1.2.2. Response quantification. Most commonly, EMG startle data are amplified and filtered during or after recording, and are then rectified and integrated or smoothed before scoring (see Blumenthal et al., 2005 for recommendations). The terms integration and smoothing are often confused since smoothing is often achieved by means of a contour-following integrator. Here, integration refers to the temporal summation of EMG activity up until an asymptote is reached, while smoothing refers to low-pass filtering of the data (Tassinary et al., 2007). Smoothing is the more common

Table 4
Overview of methodological details and considerations of verbal and psycho-physiological outcome measures commonly used in fear conditioning experiments. Note, technological advances generally allow simultaneous acquisition of (a subset of) all dependent measures but special considerations regarding conditioning protocol (e.g. effects of probed responses) and technical methodology (e.g. band-pass-filtering and/or smoothing of psychophysiological data acquired during fMRI) may apply.

Dependent measure	Response initiation	Response timing	Design considerations	Response quantification	Possible transformations and corrections	Analysis considerations	Interpretation considerations	Available guidelines and further literature
SCR	• Concurrent with stimulus onset	• Onset:1–4s • Peak within 0.5–5 s after onset (might be faster for US responses)	• Quick SCR habituation • Superimposed responses in fast stimulus sequences • Slow reaction (1–4s) • Adequate ITI and ISI • Responding to all novel/salient stimuli (e.g. startle probes, distractors) • Potential trial list effects (e.g. larger responses for first than second trial – may lead to differences between CS+ and CS- within the first two trials; larger reactions after rating blocks possible) • Can be influenced by breathing patterns	• Missing values versus zero reactions • Overlapping responses • Evaluation of the UR recommended • Negative values are physiologically not possible • Dependent on scoring approach (e.g. TTP versus GLM-based)	• Log or square root • Averaging across trials • Range corrections • T- and z-transformations • Baseline correction	• Definition and treatment of non-responders • Treatment of missing values • Transformation/range correction across multiple day paradigms • Investigation of possible group differences in UR recommended • Analyses of general response strength between groups only with raw scores • Usually employed for cued (CS+ and CS-) responses	• Conditioned SCR almost exclusively observable in contingency aware participants • Extinction success might result from extinction learning or from habituation processes	• Guidelines are available (Boucsein et al., 2012; Dawson et al., 2007)
SCL	• Modulation by stimuli onset and during conditions	• Continuously modulated	• Habituation • Assure an equal number of potentially SCR eliciting events (e.g. startle probes, ratings) during all experimental conditions (e.g. contexts) during which SCL is assessed	· Specified as average SCL of a specific time window	• Baseline correction	• Usually compares SCL for anxiety contexts versus safe contexts or baseline		• Guidelines are available (Boucsein et al., 2012)
FPS	• Probed • Usually elicited via acoustic white noise burst or air-puff	• Onset: 21–120 ms • Peak: within 150 ms after acoustic stimulus onset • Short refractory period	• Inclusion of habituation phase (2–10 startle probes) to achieve stable baseline • Physical properties of auditory startle probe should be considered • Possible interference with acquisition of contingencies[1] • To avoid predictability/preparation to the probe, jittering of the startle probe to CS/US may be employed • Can be probed during baseline conditions (ITI) and context conditions • Probing every trial or not	• Missing versus zero reactions • Negative values are physiologically not possible	• Averaging across trials • T- and z-transformation • Baseline correction	• Definition and treatment of non-responders • Treatment of missing values • Transformation/ standardization across multiple day paradigms • Analyses of general response strength between groups only with raw scores	• Probed response may have impact on the process under study[1] • CS+/CS- discrimination has been reported to occur in absence of contingency awareness	• Guidelines are available (Blumenthal et al., 2005)
HR	• Modulation by stimuli onset and during conditions	• Onset: 1–2s • Peak: 4s • Recovery: 6–8s	• Superimposed responses in fast stimuli sequences • Adequate ITI and ISI • Responds to all novel/salient stimuli (e.g. startle probes, distractors) • Influenced by breathing patterns	• Overlapping responses • Method of (e.g R wave) triggering • Trigger error detection • Treatment of last pre and post stimulus beat	• Averaging across trials • Baseline correction	• Identifying response patterns (e.g. bradycardia, tachycardia)	• Habitual response patterns (accelerators versus decelerators)	• Guidelines available (Jennings et al., 1981)

Pupillary response	• Concurrent with visual stimulus onset • Can be probed via rapid light changes in auditory conditioning studies • ('fear-inhibited light reflex')	• Onset 0.2s • Peak for probed light reflex: 0.5-1s • Short refractory period • Constant change dependent on cognitive load and emotional state	• Allows designs with short ITI • CS stimuli should have equivalent physical properties • Include fixation cross to avoid gaze shift of participants (distortion of measured pupil diameter)	• Peak change after initial light reflex • Average across a specific time-window (e.g. anticipation window before US) compared to a baseline	• Correction/Interpolation of missing data points within trials • Averaging across trials • T- and z-transformation • Baseline correction	• Treatment of missing values • Transformation/range correction across multiple day paradigms		• No clear guidelines available • Systematic review of the background and empirical literature in humans as well as some recommendations (Beatty and Lucero-Wagoner, 2000)
EEG/MEG	• Modulation by stimuli onset and during conditions	• Dependent on stimulus type (e.g. visual versus auditory) and stimulus properties (e.g. luminance, size)	• Large amount of trials needed (especially for ERPs) to raise signal-to-noise ratio to acceptable levels • ssVEFs require very specific paradigms	• Great variety in quantification methods, e.g. peak scoring versus time windows	• Averaging across trials • Low pass/high pass filtering • Artifact rejection • Ocular corrections • Baseline correction • Filtering and artefact detection methods can vary	• Time window of interest and target electrode	• Generally used to assess how sensory systems in the brain react to CS/US	• No clear guidelines available • Miskovic and Keil (2012) provide a review of electrophysiological studies of human classical conditioning (Miskovic and Keil, 2012)
fMRI	• Modulation by stimuli onset and during conditions	• Onset: 1–2s • Peak: 4–6s • Attenuated responses to stimuli presented in quick succession (~2s)	• Possible overlap of responses (CS & US, online ratings) and collinearity • Partial reinforcement, different stimuli lengths, jitter to allow for independent modelling of the hemodynamic response function • Influence of scanner context • Selection of stimulus modality (e.g. visual versus auditory in loud scanner environment)	• GLM • Independent regressors • Boxcar, FIR, stick function • Sampling of BOLD response	• Standard fMRI preprocessing • All stimulation must be accounted for in GLM (e.g. online ratings) • Careful with correction for physiological noise: possible correlation with CS/US responses	• Comparison of context versus cue (modelling of different durations/processes) • Careful model setup (parametric modelling, time series, subdivision in early and late phases)	• No inherent response criterion (additional measures should aid interpretability)	• General methodological considerations (Poldrack et al., 2008) • General recommendations of reporting on fMRI results (Poldrack et al., 2016)
Verbal reports	• After (retrospective) or during (online) visually/auditory presented questions/scales	• Restricted versus unrestricted response window	• Continuous/online versus intermittent versus post-experimental ratings • Intermittent ratings: every trial versus occasionally (after blocks of CSs) • Forced responses or possible non-responses • Response time restrictions • May mark transition between experimental phases • Possible interference with acquisition of contingencies[1]	• Free recall versus forced choice • VAS versus Likert scale versus Self-Assessment Maniquin (SAM) • Terminology considerations of scale end points (fear/anxiety versus valence versus arousal versus expectancy)	• Averaging across trials • Baseline correction	• Definition and treatment of non-responses • Individual response range	• Sensitive to experimental demand and memory bias • May impact the process under study[1] • May be dependent on contingency awareness (e.g. arousal, valence) • Retrospective ratings might be prone to memory bias	• No clear guidelines available • Considerations regarding validity of US expectancy ratings are provided by Boddez et al. (2013)

procedure to prepare the high-frequency EMG signal for the scoring process, and Blumenthal (Blumenthal, 1994) recommends a time constant of 10 ms (i.e. a cut-off frequency of 15.9 Hz). Scoring can be done manually or can be fully automated, but should always involve a clearly defined (and reported) scoring window (e.g. 21–120 ms onset latency and up to 150 ms peak latency for acoustically evoked startle blinks) as well as a minimum amplitude criterion as it will affect the number of non-responses (see 4.3.6) (Blumenthal et al., 2005). For the startle reflex, it is particularly important to discriminate between non-responses and missing values. Non-responses are scored with an amplitude of zero and contribute to mean calculations. However, missing values, that is trials showing recording artefacts or distorted amplitudes due to probing during the muscle refractory period following a spontaneous eye-blink, do not contribute to mean calculations (see Blumenthal et al., 2005). Furthermore, double peaks are observed in some participants and it has been suggested that the second peak corresponds to the startle reflex whereas the first peak represents an auditory blink reflex (Meincke et al., 2002).

In differential conditioning procedures (see 3.2.1), FPS is usually indexed by the difference of the startle responsivity during the presentation of a CS+ and the CS- (CS discrimination) accompanied by difference scores between startle responses during the ITI and responses during the CS+ (CS+ potentiation) and CS- (CS- potentiation). The latter allows for additional consideration of differences in the startle responding to the CS- and/or differences in the overall startle reactivity between groups.

4.1.2.3. Transformations and corrections. FPS scores can be based on raw data differences, standardized data differences (e.g. T-transformation or z-transformation), or percent-change scores. Importantly, recent results of a direct comparison between these quantification methods suggest that FPS (assessed during a US-threat task) may be most reliable if based on raw data differences (Bradford et al., 2015), while percent-change scores are generally not recommended by the authors. Importantly, even though data analyses may be primarily based on transformed data, raw data should always be consulted additionally. Importantly, group differences in general reactivity (startle amplitude) cannot be investigated using transformed data, as transformations eliminate the related variance.

4.1.3. Heart rate

Changes in HR as a measure of human fear CRs were commonly employed, particularly in the early years of fear conditioning research (see Cohen and Randall, 1984, for a review). Both conditioned HR decelerations and conditioned HR accelerations have been observed with the former presumably indicating an orienting response to the signal value of the CS and the latter a defensive response and, thus, reflecting learned fear (Hamm et al., 1993). Accordingly, conditioned HR decelerations are observed more commonly with neutral CSs (Lipp and Vaitl, 1990), whereas conditioned HR accelerations are associated with fear-relevant CSs and more intense USs (Dimberg, 1987; Hamm et al., 1993). Moreover, individuals differ regarding their habitual HR responses with some showing decelerations and some showing accelerations to the same stimulus (Hodes et al., 1985). Taken together, conditioned HR changes seem to reflect the stage of the defense cascade that is dominant during CS processing (Lang et al., 1997) which should be carefully considered during planning the experiment.

Similarly, onset and peak latencies of HR responses are dependent on experimental parameters such as stimulus intensity and modality (reviewed by Cook III and Turpin, 1997). For visual CSs, which are most commonly used in human research, average onset, peak, and recovery latencies typically occur within 1–2s, about 4s, and 6–8 s respectively (e.g. Hamm et al., 1993; Hodes et al., 1985; Panitz et al., 2015). To avoid superimposed HR responses by subsequent US, CS, or startle probe onsets, such values have to be taken into account during study design planning. For further information on HR recording and quantification we refer the interested reader to published guidelines for HR studies in humans (Jennings et al., 1981).

4.1.4. Pupillary response

The human pupillary response has also been described as a reliable measure for CRs (Bitsios et al., 2004; Reinhard et al., 2006; Reinhard and Lachnit, 2002) and can be easily assessed by eye-tracking or pupillometry in the behavioural laboratory as well as during fMRI acquisition. In contrast to slow SCRs, the pupillary response, which is innervated both sympathetically and parasympathetically (Granholm and Steinhauer, 2004; Steinhauer and Hakerem, 1992), is fast and reflects a measure of psychological arousal (Granholm and Steinhauer, 2004). Pupil dilation is characterized by response onsets as fast as 0.1–0.2 s (Beatty and Lucero-Wagoner, 2000) or 0.3–0.4 s (Kuchinke et al., 2007) allowing for paradigms with short ITIs/ISIs and circumventing superimposed reactions due to subsequent stimuli (e.g. startle probes, US).

With respect to fear conditioning, pupillary responses can be measured continuously (e.g. in experiments employing visual CSs) or can be probed by brief light stimuli (e.g. in experiments employing auditory CSs). Importantly, illuminance-related changes in pupil dilation are mediated via a well described midbrain circuit (McDougal and Gamlin, 2008) whereas the precise anatomical route of non-illuminance-related changes has not yet been established (cf. Korn and Bach, 2016). Yet, it has been proposed that both share a final common muscular and neural pathway (cf. Korn and Bach, 2016).

In case of continuous measures, the appropriate time window for response quantification needs to be specified. Thereby, a time window directly after CS onset as well as a time window representing an anticipatory phase prior to US administration has been employed for the detection of CS-discrimination in fear conditioning studies (e.g. Greenberg et al., 2013; Reinhard et al., 2006; Reinhard and Lachnit, 2002; Visser et al., 2013). The probed light reflex (peaking at 0.5–1 s after light onset) has been proposed as a potential analog to the FPS reflex showing decreased pupillary constrictions following (auditory) CS+ presentations ("fear-inhibited light reflex"; Bitsios et al., 2004). In addition, pupillary responses can be quantified in terms of *mean* or *peak* pupil dilation to a mean baseline pre-stimulus interval (typically between 0.2–1s).

Contrary to SCRs, clear guidelines with respect to general study design (e.g. control for stimuli luminance, CS assignment), response quantification and processing (e.g. transformations) of pupillary data are not available to date, although a formal quantitative model for pupil responses has recently been suggested (Korn and Bach, 2016). Interested readers are referred to Beatty and Lucero-Wagoner (Beatty and Lucero-Wagoner, 2000) for a systematic review of the background and empirical literature in humans as well as some recommendations (e.g. treatment of missing data points due to eye-blinks) and to a comprehensive survey of sources of variation in pupillometry (Tryon, 1975).

4.1.5. Electroencephalography/magnetoencephalography

Apart from the above stated techniques, scalp-recorded EEG and MEG have been used as a neurofunctional index of fear CRs. Both electro-cortical techniques measure synaptic activity at the dendrites (Olejniczak, 2006) and allow for assessment of the cortical (but not subcortical) function during fear conditioning with a very high temporal (within ms) but limited spatial resolution of cortical areas only (Miskovic and Keil, 2012). In comparison to the study of startle, SCR or the pupillary response, EEG/MEG studies are typically performed to gain insight into how sensory systems in the brain

(visual and auditory) react and adapt to fear CSs. This can be done by recording the immediate neural response to CSs in the cortex by means of event-related potentials (ERPs) or event-related field time averaged responses (ERFs) (Stolarova et al., 2006). Another frequency-based variant of ERPs are steady state visually evoked potentials (ssVEPs) and their magnetic counterpart, the steady state visual evoked field (ssVEF) (Moratti et al., 2006; Vialatte et al., 2010). ERPs and ERFs are typically used as an index of sensory or attentional function in the cortex, and both differentially increase (CS+ vs. CS-) after fear acquisition training (Miskovic and Keil, 2012; Moratti et al., 2006) and the extinction thereof (Mueller et al., 2014) has been demonstrated for the visual cortex and the auditory cortex (Bröckelmann et al., 2011).

However, usage of EEG/MEG to assess fear CRs as measures of perceptual stimulus processing has some inherent difficulties. First of all, due to the nature of EEG data, neurofunctional targets are limited to cortical networks. Second, EEG and MEG are highly sensitive to perceptual features of the presented stimuli (Bradley et al., 2007). As such, the location at which the CS signal is measured and its magnitude depend on the modality of the presented stimulus and on its perceptual properties, such as size, duration, or luminance. Therefore, careful stimulus selection and design is crucial to disentangle purely stimulus-related EEG/MEG activity from a conditioning-driven EEG/MEG signal. Third, classical ERP analysis requires a large amount of trials per condition (often >50) (e.g., Sperl et al., 2016) to raise the signal-to-noise ratio of EEG/MEG data to acceptable levels, which is atypical for fear conditioning studies and can strongly restrain protocols. This is a particular problem when the research question concerns the state or the speed of fear and extinction learning for which more or less steep learning curves are observed that preclude measuring many trials that elicit the same stable state. Of note, some studies have applied single-trial EEG analysis within fear conditioning paradigms (e.g., Wieser et al., 2014) to evaluate fast-paced changes in cortical activity. Readers interested in EEG/MEG during fear conditioning are referred to Miskovic & Keil (Miskovic and Keil, 2012) for an excellent review of the empirical literature, methodological issues, and further guidelines and recommendations.

4.1.6. Functional neuroimaging

Since the first event-related fMRI studies on classical fear conditioning in humans (Büchel et al., 1998a,b; LaBar et al., 1998), this line of research has produced a number of narrative reviews (Büchel and Dolan, 2000; Haaker et al., 2014; Kim and Jung, 2006; Myers and Davis, 2007; Sehlmeyer et al., 2009), translational reviews (Etkin and Wager, 2007; Maren, 2001; Milad and Quirk, 2012; Patel et al., 2012; Rauch et al., 2006), and meta-analyses (Diekhof et al., 2011; Fullana et al., 2015; Mechias et al., 2010) that provide a comprehensive source of reference with respect to the neural networks involved in fear conditioning. Here, in turn, we focus on a methodological discussion of fMRI specifically for fear conditioning as well as related processes with respect to study design and analysis. Complementing other dependent variables, fMRI can serve as a basis for further inference on underlying mechanisms that may be targeted with a large range of evaluation techniques including mass-univariate, connectivity, and multivariate analyses.

4.1.6.1. Paradigm considerations. An efficient fMRI design has as many scans as possible. It only contains the number of conditions necessary, which are optimally two identical conditions that differ only in terms of one single dimension: the experimental manipulation (Garavan and Murphy, 2009; Henson, 2007).

Standard fMRI evaluation is based on the GLM, which relies on independent regressors (Friston et al., 1995; Worsley and Friston, 1995). Collinearity between regressors decreases with increasing variance between the regressors. In a typical conditioning experiment with a CS+, a CS- and a US, this can be achieved by careful computation of transition probabilities between CS+ and CS- trials. For fixed-order effects of a CS+ and US, the decorrelation between the CS+ and US can be obtained by a longer CS+ duration [6–8s, assuming condition regressors of stick functions at the onset of the CS+ and US convolved with the hemodynamic response function (hrf)] before US onsets, jittered onsets of the US in relation to the CS+, partial reinforcement of 80% or less, or a combination of those (Henson, 2007). Dependent CS+/US regressors (i.e. no jitter *and* 100% reinforcement) may reduce the quality of parameter estimates (Mumford et al., 2015) which may be considered during study design. In case of fully dependent CS+/US regressors, folding of the hrf with a box-car with CS+ duration may be an alternative to stick functions, which rather model discrete events. However, it will not be possible to separate CS+ and US activation statistically, and hence, this should already be considered during design. Although many behavioural and psychophysiological paradigms might already be efficient as an fMRI design, it has proven invaluable to investigate the impact of small changes (e.g. breaks) and compute collinearities between regressors *a-priori*.

Temporal dynamics of a learning paradigm, parallel evaluation of all dependent variables, or advanced analyses techniques increase the need for reliable estimations on the basis of few or single trials. This is only enabled on the basis of the design. Here, trial pseudo-randomizations limit effects of order, balanced transition probabilities reduce expectancy effects, while a controlled jitter or oversampling of stimulus onsets relative to image acquisition avoids a sampling bias (once sampling at the peak and once not) in any condition.

Finally, the fMRI setting needs to be considered during stimulus selection and construction. Picture qualities such as brightness and contrasts deviate between screens and projectors, the perception of sounds might be affected by scanner noise (Gaab et al., 2007). Similarly, motor responses (e.g. US expectancy ratings) will lead to motor activation (and thus should be present in all or no conditions). As the cognitive evaluation of the CSs (i.e. ratings) and US calibrations most likely depend on the context (Price, 2000), these should therefore also be carried out within the scanner.

Depending on the protocol, short scanning sessions within the experiment may be advantageous for accurate data acquisition, however any scanner break can affect learning speed and success through the perception of an experimental break (in particular, when coinciding with the transition between experimental phases).

Besides general considerations about conducting and reporting fMRI studies (Poldrack et al., 2008; Thulborn et al., 1996), specific interactions of the fMRI scanner environment with emotional paradigms need to be taken into account. In itself, the scanner bore is a noisy, distracting, or even threatening and inescapable context that interacts with experimental manipulations (Elliott et al., 1999; Gutchess and Park, 2006; Hommel et al., 2012; Pripfl et al., 2006; Skouras et al., 2013). Hence, individual reactions to the environment have the potential to pose a confounding factor on average and group effects (Mutschler et al., 2014), data quality in patient samples (Lueken et al., 2011) and transitions form the behavioural lab to the scanner environment need to take this into account. A reduction of these effects can be achieved by scanner habituation before and at the beginning of the experiment, clear and demonstrative instructions on how to avoid head motion, comfortable bedding, and careful selection of control participants (e.g. not only on age and sex, but also on scanner experience).

4.1.6.2. Analysis considerations. In a typical conditioning experiment, CS+ and CS- trials are presented pseudo-randomized in an event-related design (Dale and Buckner, 1997; Friston et al., 1998; Josephs et al., 1997). In general, conditioning experiments do

not require a special pre-processing pipeline. Task-related motion, caused by US or startle probes, needs to be checked and corrected for to limit the risk of false activations in the fMRI analysis due to intensity variations (Friston et al., 1996; Hajnal et al., 1994). Since adding motion covariates (e.g. obtained from realignment) to the first-level model may reduce sensitivity (while enhancing specificity) (Johnstone et al., 2006), alternative approaches such as independent component analysis might be considered (Kochiyama et al., 2005; Pruim et al., 2015). Many fMRI scanner environments provide an opportunity to obtain data on respiratory and cardiac functioning, which might cause non-neuronal blood-oxygen-level dependent (BOLD) changes (Birn et al., 2009; Chang et al., 2009; Glover et al., 2000). However, as respiratory and HR responses are also subject to fear conditioning, physiological noise removal should be applied with care (Glover et al., 2000), as it may remove genuine effects.

Effect sizes in model-based fMRI analyses depend on the model, which itself depends on the hypotheses. For example, a model that proposes longer underlying processes would convolve the hrf with boxcars, while short processes would be hypothesized with a standard hrf at the onset of a stimulus. Consequently, collapsing regressors, because they are collinear, e.g. combining dependent CS+/US regressors and models from CS+ onset to US offset, might lead to difficulties in the selection of an appropriate temporal model for such a trial. Here, two stick functions to the onsets of CS+ and US, respectively, might be more suitable to model independent effects (see Mumford et al., 2015 on how to deal with colinearities; O'brien, 2007).

FIR-models or model-free analyses such as Principal or Independent Component Analysis might help to explore the data in more complex designs and may aid in the definition of an appropriate model for a GLM analysis.

In addition to standard univariate or voxel-wise analysis contrasting mean activations between conditions, learning paradigms can profit from an investigation of temporal dynamics and parametric influences (Büchel et al., 1998a,b). In both cases, an additional regressor defines the expected changes of BOLD amplitude for every instance of onset of a condition, e.g. related to habituation or adaptation (Marschner et al., 2008), US expectancy ratings or SCR amplitudes (Geuter et al., 2014), attention (Straube et al., 2007), or learning models (Rescorla and Wagner, 1972). Furthermore, recent evaluation techniques such as multi-voxel pattern analysis, e.g. parameter estimates of conditions or single trials (Mumford et al., 2014), allow researchers to test how distributed patterns of BOLD activations across multiple voxels relate to experimental variables (Davis et al., 2014; Visser et al., 2011, 2013).

4.1.6.3. Considerations for acquiring psychophysiological measures within the MR-environment. Generally, fear- and anxiety-related changes in neural activation should always be accompanied and related to other behavioural or physiological measures to aid interpretation of the data (Wong et al., 2011). However, if acquired in parallel to fMRI, physiological signals are prone to magnetic induction due to the movement of conductive cables and electrodes, rapid switching of MR gradients, and radio frequency (RF) emitted by the RF coil (Gray et al., 2009; Wong et al., 2011). Hence the set-up requires special care as well as specific MR-compatible equipment (Lemieux et al., 1997), correct and thorough wire-management (no loops, running in parallel, and using face caps) as well as exact synchronization with the MR scanning to improve safety and signal quality (Gray et al., 2009).

For EEG/EMG/startle data (e.g. Lindner et al., 2015), imaging artefact removal is indispensable and can be achieved through numerous methods and software (Allen et al., 1998, 2000; Garreffa et al., 2003; Mantini et al., 2007; Niazy et al., 2005; Ritter et al., 2007; Ullsperger and Debener, 2010). As the SCR signal is considerably slower (and is not obtained directly within the field-of-view), high-pass filtering is usually sufficient even though smoothing may further facilitate response quantification. Furthermore, the pupil diameter (see 4.1.4; Visser et al., 2013) and infrared oculography (Anders et al., 2004) provide alternative methods for response quantification in the MR environment, as eye-tracking in the MR environment is less susceptible to noise due to lossless signal transduction with optic fibres (Kimmig et al., 1999).

Care should also be taken with respect to effects of psychophysiological recordings on fMRI images, such as local signal drop out and magnetic susceptibility differences may occur close to cables, electrodes, and electrode gel; however, they are manageable (Krakow et al., 2000). Shielding and high frequency filters prevent degradation of the image signal-to-noise-ratio due to electromagnetic noise from the recording equipment. It is recommended to evaluate the interaction of fMRI and physiology measurement for every composition of equipment and fMRI protocol (Krakow et al., 2000).

4.2. Verbal report measures of fear learning

Verbal report measures encompass both cognitive (ratings of CS-US contingencies or 'risk') and affective (ratings of valence, arousal, fear/anxiety, and liking associated with a CS) components. The following paragraphs elucidate the methodological and interpretative aspects that have to be considered when planning to assess subjective outcome measures in human fear conditioning.

4.2.1. Conditioned stimulus – unconditioned stimulus expectancy and contingency ratings

In a differential fear conditioning design, contingency awareness refers to the ability to explicitly discriminate between the CS that was followed by the US, and the CS that was not, with accuracy above chance level. Similarly, in single-cue designs the CS should be recognized as predictive of the US.

Contingency awareness can be inferred by means of ratings of CS-specific US expectancy that is commonly indicated by dichotomous forced choices (expected/not expected), visual analog scales, Likert scales, or special devices (Boddez et al., 2013). Continuous (online ratings; i.e. during CS presentations) or intermittent assessment of contingency represent probability estimates of the upcoming US, and hence, might be interpreted as risk-estimates. As such, these ratings may have a high predictive value as risk overestimation is a critical feature in pathological anxiety. Ratings of CS-US contingencies however may draw attention to possible CS-US contingencies and may influence (i.e. boost) the learning process itself. In other words, such concurrent ratings may 'create contingency awareness rather than measure it' (cf. Baeyens et al., 1990 for evaluative conditioning), even though this has not yet been systematically investigated.

Ratings of US expectancy/CS-US contingency however provide the advantage of allowing for the identification of 'a point of subjective CS discrimination'. In line with this, trial-by-trial ratings of US expectancy, as an index of conscious CS-US contingency knowledge, has been shown to align with the development of CRs in time (Purkis and Lipp, 2001; Weidemann et al., 2016; Weidemann and Antees, 2012).

Post-experimental assessment of CS-US contingency ratings by a retrospective questionnaire (Bechara et al., 1995), in turn, may lead to an underestimation of contingency awareness (i.e. 'forgetting'), in particular, when assessment does not take place directly after acquisition, but after extinction (discussed by Lovibond and Shanks, 2002) in case of single day paradigms. Thereby, assessment procedures range from free recall (e.g. 'Did you know when you were going to receive an electro-tactile stimulus?') to forced choice recognition procedures ('Was Picture X or Picture Y more often followed by the electro-tactile stimulus?'). Based on this

information, participants are commonly classified as 'aware' or 'unaware' of CS-US contingencies. Notably, no standard procedure with respect to CS-US contingency awareness assessment and subsequent classification exists to date. We refer the interested reader to a comprehensive discussion of the reliability and validity of contingency awareness measures as well as the relationship between contingency awareness and differential CRs across measures (Boddez et al., 2013; Lovibond and Shanks, 2002; Wiens and Ohman, 2002).

Thereby, the nature of the association between contingency/risk perception and CS discrimination learning depends both on design specifications and the outcome measures. For instance, it has been argued that contingency perception is only necessary in order for trace conditioning to occur, but not for delay conditioning (Clark et al., 2002; Weidemann et al., 2016; Manns et al., 2002). Furthermore, CS discrimination in FPS as well as amygdala activation does not seem to require explicit contingency awareness (Hamm and Weike, 2005; Tabbert et al., 2011 even though this has not always been observed; see) (Baas et al., 2008; Baas, 2013) while CS discrimination in SCRs (e.g. Hamm and Vaitl, 1996; Sevenster et al., 2014; Tabbert et al., 2011 and evaluative conditioning: De Houwer et al., 2001; Field, 2000a,b; Fulcher and Hammerl, 2001) seem to be conditional on contingency knowledge.

In conclusion, the acquisition of CS-US contingency ratings is indispensable when interested in a subjective measure of learning success, e.g. when the research question addresses successful learners only (see 4.3.4; performance-based exclusion criteria). Therefore, trial-based online-ratings of US expectancy have been suggested to be more valid and reliable than post-experimental assessments (cf. Lovibond and Shanks, 2002) even though online-ratings may, in principle, interfere with the process under study (i.e. evolvement of learning). We refer the reader to other sources for an in-depth discussion of US expectancy and CS-US contingency ratings as well as methodological considerations thereof (Boddez et al., 2013; Lovibond and Shanks, 2002).

4.2.2. Affect ratings

In addition to CS-US contingency ratings, CSs can be evaluated in terms of valence ('How positive/negative is the symbol for you?'), arousal ('How arousing is the symbol for you?') (Bradley and Lang, 1994), fear/anxiety ('When you see this symbol, how strong is your fear/anxiety?'), the liking of a stimulus (evaluative conditioning; see De Houwer (2007) for a review) or distress 'How distressed do you feel when you see this symbol'). Thereby, visual analog scales or Likert scales as well as the Self-Assessment Manikin (SAM) (for valence & arousal; Bradley and Lang (1994) are widely applied.

Similar to the assessment of CS-US contingency ratings, these ratings can be provided online, after each trial, intermittently (i.e. after blocks of trials) or retrospectively.

Importantly, while online ratings (e.g. Marschner et al., 2008) may be advantageous for the modelling of learning rates (see 4.3.7), the cognitive and motor components of rating procedures may interfere with physiological and neural measures of CRs. Hence, a careful timing of rating procedures (particularly online and intermittently presented ratings) with respect to other measures and transitions with other experimental phases is essential. Recently, it has been shown that intermittently presented fear ratings during uninstructed acquisition did not significantly impact CS-discrimination as compared to a group without ratings, even though there was suggestive evidence that ratings may facilitate fear learning (Sjouwerman et al., 2016). A study comparing groups of participants that were asked to either provide valence ratings postexperimentally or intermittently (i.e., every three trials resulting in one rating during mid-acquistion and one rating at the end of acquisition) did also not observe any differences in CS+/CS- discrimination in SCRs between groups (Blechert et al., 2008) during acquisition that involved direct instructions on CS-US contingencies (i.e., one of two pictures will sometimes be followed by the US but the second never). It can thus be speculated, that trial-by-trial or online (i.e., continuous) ratings may exert a more substantial impact on fear conditioning processes in particular when no information on CS-US contingencies are provided explicitly (see 2.2.4).

Furthermore, ratings during fear conditioning may generally interact with the development of contingency awareness (see 4.2.1), unintentionally trigger other memory processes (i.e. reconsolidation after reactivation through CS+ presentation during the rating; Schiller et al., 2010), or directly influence the strength of the developing CR due to the emotion regulating effect of affect labelling (Lieberman et al., 2007). Additionally, ratings are subject to task-demands and reporting biases due to experimenter and other effects.

Taken together, the value of including ratings during the experimental learning phases should be carefully balanced against the possible impact of rating procedures on the time course and strength of learning for the specific research question.

4.3. General analysis considerations for fear conditioning research

4.3.1. Multiple outcome measures

Simultaneous recordings of multiple indices of fear learning/expression are increasingly being employed and can generally be advocated due to the increase in information from multiple sources, which partly tap into different processes. Thereby, however, some theoretical and methodological consideration should not go unnoticed.

First, different outcome measures may represent different dimensions of fear learning. Thereby, the dual-process account of fear learning (Hamm and Vaitl, 1996; Hamm and Weike, 2005; Sevenster et al., 2012) assumes distinct learning processes underlying affective and expectancy learning respectively. Hence, both measures are not necessarily expected to converge. For instance, SCRs are thought to be closely related to arousal ratings, whereas startle responses are modulated by valence (Bradley et al., 1999). Moreover, particularly SCRs and FPS have been differently associated with additional experimental variables during fear conditioning such as contingency awareness (see 4.2.1) and instruction (see 2.2.4: Sevenster et al., 2012). Others have however assumed both affective and expectancy learning to originate from identical learning systems (Lipp and Purkis, 2005; Lovibond, 2004; Lovibond and Shanks, 2002). In case such different predictions exist with respect to multiple indices of conditioned responding or if one outcome measure serves as the primary measure, a correction for multiple comparisons is generally not necessary (Feise, 2002). Controlling for Type I (alpha) error may however be warranted in case of a disjunction of statistical hypotheses for different outcome measures (i.e. the empirical hypothesis is true when a significant effect is observed for conditioned SCRs *or* FPS, *or* both). Alternatively, different outcome measures might be incorporated into one global model, for instance, by employing structural equation models (SEMs) (Kuhn et al., 2016), Bayesian hierarchical modelling (Onat and Büchel, 2015), combined probability tests (e.g. Fisher's or Brown's method Brown, 1975), representational similarity analysis (Cichy et al., 2014), as well as classification approaches (Hogervorst et al., 2014).

Second, read-outs of multiple outcome measures may interfere with each other when simultaneously acquired. For instance, in case of simultaneous FPS and SCR measurement, a rather long CS duration is required to assure that SCRs to the CS onset is not confounded by SCRs elicited by the startle probe (see also 4.1.1.1). Such superimposed SCRs have often distorted amplitudes and temporal characteristics (Dawson et al., 2007). Considering a typical SCR

latency of 1–4 s (Dawson et al., 2007), a minimum interval between the startle probe and a preceding CS should be 5.5 s after CS onset. An alternative for short CS durations is to include trials in which the startle probe is omitted (e.g. 50% trials with and without the startle probe) and analyse SCRs only in the non-startle trials. In addition, a delay of approximately 6–10 s between an ITI startle probe and subsequent CS onset is needed to ensure sufficient recovery time for the SCR elicited by the ITI startle probe (Grings and Schell, 1969).

Despite of careful timing, it has recently been shown that inclusion of startle probes, but not intermittently presented fear ratings, delay and attenuate conditioned responding (i.e. CS+/CS- discrimination, Sjouwerman et al., 2016). Hence, the inclusion of different outcome-measures may interfere not only with each other, but they may also interrupt and alter the process under study.

4.3.2. Multiple day paradigms

Following the increasing appreciation of differences between immediate and delayed extinction protocols (see 3.4.1), and fear and extinction recall, as well as the general importance of memory consolidation, multiple day paradigms have recently gained more popularity. Thereby, fear acquisition training, extinction training, as well as ROF manipulations and tests are separated by time (e.g. 24 h or more) which requires not only different design considerations but also specific analysis and interpretational considerations compared to those required for single day paradigms.

First, subtle details of the experimental procedure may promote either dominance of the fear or the extinction memory trace at a later test. More precisely, a re-attachment of US-delivering equipment is important to maintain credibility and may promote fear recall, while the removal/non-attachment of US-delivering equipment may promote extinction recall. Similarly, in multiple day paradigms, US intensity may or may not be re-calibrated individually, either prior to fear acquisition or prior to every experimental session. Importantly, US-recalibration prior to extinction (recall) and ROF tests may induce reinstatement-like effects, which may crucially bias responding (Haaker et al., 2014) or may reduce reinstatement effects by deflating the US memory, which may have become inflated overnight. On the other hand, the pain-threshold is sensitive to a large number of factors such as hormonal variations (Riley et al., 1999), stress (Butler and Finn, 2009), or fear and anxiety (Rhudy and Meagher, 2000). Therefore, re-calibration may be reasonable for certain research questions/designs.

Second, instructions in multiple day paradigms are important as they may boost either fear recall (e.g. 'Yesterday you received the aversive event occasionally. Today, you will undergo a similar experiment') or extinction recall (e.g. 'Yesterday you experienced the aversive event, but today, you will not').

Third, potentially variable external (e.g. electrode placement, temperature, humidity, and time of day) or internal (e.g. sleep-, hormone-, or mood-related) factors may impact the CRs, and therefore, should be controlled for carefully.

Third, transformations (e.g. T-transformation) and corrections (e.g. range-correction) may be performed separately for each experimental day or across days. Thereby, responding may be inherently different with respect to the maximum and range of responding. Hence, data post-processing may better focus on the data acquired within a single day even though a direct comparison of CRs across days (see also 4.3.5) may be desirable. Direct across-day comparison is however hampered by possible influences of response habituation (i.e. floor effect) occurring by the end of an experimental day and orienting responses (i.e. ceiling effect) at the beginning of a new experimental day. For ROF tests, including a brief re-extinction phase prior to the ROF manipulation and test (Haaker et al., 2014) can avoid problematic across-days comparisons that are particularly relevant for physiological measures.

4.3.3. Statistical quantification of conditioned responding

In human differential designs, CS+/CS- discrimination represents the most critical statistical index across acquisition training, extinction training, and the ROF test. As such, CS discrimination reflects learning-related effects while controlling for general responsivity. Group differences in CS discrimination should however always be accompanied by CS-specific analyses to aid interpretation of the results. More precisely, CS- related differences may indicate differences in safety learning (i.e. inhibitory processes), while CS+ related differences in turn are indicative of differences in fear learning (i.e. excitatory processes). The sole report of CS+ specific analyses, despite of a differential design, is inappropriate as results may simply reflect general responsivity rather than learning-related changes.

It is important to note that studies differ greatly in terms of the time bin that is used for the quantification of learning. Some authors calculate mean (differential) responding across a full experimental phase, whereas others use the start-point or end-point performance (i.e. mean across a limited number of single trials) or consider temporal dynamics (see 4.3.7). While mean responding across an experimental phase includes responding in trials before fear learning was successful, and hence, may underestimate an effect, the restriction to an (arbitrary) number of single trials may overestimate an effect.

Further, some authors routinely exclude the first trial of acquisition and/or extinction training for each CS from the analyses arguing that learning could not have occurred yet. Investigations on the trial-by-trial evolvement of extinction learning, however, would require consideration of this trial as well, as it may carry important information, particularly in multiple day experiments where the first trial(s) of extinction occurring on Day 2 has been conceptualized as testing for fear recall (see Table 2).

Currently, the resurrection of Bayesian statistics (see Miltiadis-Krypotos et al., 2017 for an introduction tailored to human fear conditioning research) as an alternative to frequentist or classical test statistics offers feasible possibilities of testing for the probability of a difference (or lack of difference). Here, the decision for an alternative hypothesis grounds on its predominance over the null hypothesis. Importantly, Bayesian statistics may also provide statistical evidence for equality between CS types or groups, which may never be inferred from rejection of the null hypothesis on the basis of type I errors in frequentist statistics (i.e., with p being larger than the alpha level).

4.3.4. Performance-based exclusion of participants

Studies widely differ with respect to exclusion of participants based on experimental outcome parameters such as end-point performance (i.e. CS+ > CS-) during acquisition/extinction training or cognitive CS-US contingency awareness (see 4.2.1). Such exclusion or stratification is not routinely employed but may be reasonable for specific research questions. For instance, the effect of pharmacologically enhanced extinction learning/consolidation has been shown to be contingent on genuine learning experiences and/or extinction success (i.e. end-point extinction performance). More precisely, the beneficial effects of drugs enhancing extinction memory consolidation and exposure treatment were only observed in animals (Bolkan and Lattal, 2014; Bouton et al., 2008; Weber et al., 2007) and humans who did demonstrate successful extinction learning/treatment response to cognitive-behavioural therapy (CBT) (Smits et al., 2013a, 2013b, 2014; Telch et al., 2014). Importantly, the opposite effect (i.e. fear enhancing effect) was observed in those not successfully extinguishing.

While reasonable in some cases, performance-based exclusion can be problematic. First, exclusion based on end-point performance, such as CS+/CS- discrimination, requires a specific cut-off criterion. As no clear guidelines and validated cut-off criteria exist,

there are substantial 'researcher's degrees of freedom' inherent in the performance-based exclusion of participants, which are not seldom leading to extensive discussion during the peer-review processes (i.e. how to define an 'extinguisher' vs. 'non-extinguisher'; 'responder' vs. 'non-responder'). In fact, cut-off criteria in the literature do not only differ across labs but also across different studies within the same lab, which challenges both replication and comparability. For instance, a minimum (arbitrary) discrimination score (i.e. <0.01 μS or 0.02 μS for SCRs) might be based on the entire acquisition phase, the second half of acquisition, or the last trial only.

Second, performance-based exclusion criteria can lead to exclusion-rates that may easily exceed 50% of the initial sample, which may challenge the applied cut-off criteria, the study design, or response quantification (or all of them), and thus, limits the generalizability of the results.

Third, as studies commonly employ more than one outcome measure for CRs (see 4.3.1), performance-based exclusion of participants is complicated by the fact that performance-based cut-off scores across measures may not necessarily converge. In fact, 'the failure of the FIR (i.e.FIR of the SCR; see 4.1.1.2) to exhibit a contingency effect does not permit the inference that the subject is not able to verbally report this information, nor does it permit the inference that alternative measures would not reflect this contingency' (cf. Prokasy, 1977 (p. 362)) has been known for decades. Furthermore, it is not clear which outcome measure is suited best to determine the reliable and valid performance-based exclusion criteria.

Fourth, while the application of performance-based exclusion criteria may reduce variance, an important draw-back comes with highly selected samples. This inevitably constrains the generalizability of the results and induces considerable variance between studies, which may ultimately result in non-replication and interpretation problems. For instance, different and even opposite effects (see above) when excluding or not excluding participants that do not extinguish to a certain criterion have been reported in the same dataset (Golkar and Öhman, 2012). Importantly, end-point performance may in fact carry meaningful information rather than merely reflecting 'noise'. Hence, such a highly selective pre-selection of participants may be particularly problematic for studies targeting individual differences (see 5.3). For instance, a variant of a polymorphism in the serotonin transporter gene (*5-HTT*LPR s-allele) has been described as an individual difference factor associated with the success of CS discrimination during fear acquisition training (Lonsdorf et al., 2009; Lonsdorf and Kalisch, 2011). Thus, pre-selection based on CS discrimination likely induces a selection bias in favour of individual difference factors, promoting strong CS discrimination (i.e. *5-HTT*LPR s-allele), which has been demonstrated in a prior report (Garpenstrand et al., 2001).

Clearly, the field needs guidelines and recommendations with respect to these issues that have to be derived from experimental work specifically targeting aspects that allow 'high researcher's degrees of freedom'. Until progress has been made in this respect, we highly recommend that authors, in case their specific research question requires performance-based exclusion of participants, should 1) report the precise criteria used for this definition, including the number of trials the value is based on; 2) report a rationale; and 3) briefly report whether the reported results remain comparable if these exclusion criteria are not applied (i.e. a sensitivity analysis). For now, we explicitly do not recommend performance-based exclusion of participants as a standard procedure.

4.3.5. Correcting for preceding within-session performance

Performance during extinction and ROF tests can hardly be interpreted in isolation because responding may at least partly depend on learning success during preceding experimental phases. Hence, even though hypotheses may exist specifically with respect to one experimental phase, outcome during preceding phases needs to be reported briefly, which is particularly important in studies focusing on between-group effects (see 5.3).

Some authors have suggested correcting for performance during preceding experimental phases (e.g. 'recovery index'). This suggestion is similar to the performance-based exclusion of participants; however, it is not necessarily unproblematic as it is based on the assumption that 'performance during training' can be equalized with 'learning'. Importantly however, memory research has comprehensively shown that 'learning happens over intervals in which there are no changes in performance, and that little or no learning can happen across intervals in which there are substantial changes in performance' (cf. Craske et al., 2008)

With respect to fear conditioning, rodent research has shown that within-session extinction and between-session extinction are not correlated (Plendl and Wotjak, 2010), and that behavioural or physiological indicators of fear during extinction training do not predict performance at a later test in rodents (Bouton et al., 2006a,b; Shumake et al., 2014) and humans (Prenoveau et al., 2013). Similarly, neither within-session fear reduction, which can be considered a clinical equivalent to within-session extinction, nor extinction-end-point level of fear predict therapy success (for a review see Craske et al., 2008).

In fact, it is assumed that fear responding during a test is a function of the dominance of the previous fear memory and the subsequently acquired inhibitory safety memory trace (Myers and Davis, 2007). Hence, performance during the test is likely determined by the strength of and interaction between both the memory traces, the factors' time, the context, and the consolidation processes.

Notably however, there is also evidence that performance may critically depend on responding during previous experimental phases. The most prominent example comes from work on d-cycloserine, which is assumed to be a cognitive enhancer for extinction learning and cognitive behavioural treatment, and was shown to facilitate long term extinction/exposure efficacy only if within-session learning was achieved (Rothbaum et al., 2014; Smits et al., 2013b, 2013b).

In sum, adjusting for within-session or end-point performance is not necessarily unproblematic, and hence, if such corrections are applied, we suggest accompanying them by results based on non-corrected data or single-trial graphs to allow for a comprehensive interpretation of the data. Furthermore, if corrections are applied, we suggest relying on differential scores (i.e. CS+/CS- discrimination) rather than merely CS+ related corrections to allow investigating genuine learning-related processes from all response levels. An additional consideration is the number of trials (e.g. last two trials during extinction) employed for such corrections, for which no general recommendation is available. Notably however, the impact of such corrections will critically depend on the total number of trials in the experimental protocol. For instance, responding during the last two trials of extinction can be expected to be substantially different in case of a total number of 5 versus 50 extinction trials. Similarly, correcting for preceding performance is not recommended as a standard procedure and requires careful considerations and reporting of 1) precise criteria, 2) a rationale, and 3) carefully conducted control analyses (e.g. reporting of results when not employing corrections or presentation of single-trial graphs).

4.3.6. Definition and treatment of zero-responses and missing values

Similar to the performance-based exclusion of participants (see 4.3.4), the exclusion and definition of non-responders is a matter of concern. Non-responses refer to responses that fall below a

specific cut-off criterion (e.g. SCRs falling below a minimum amplitude criterion such as 0.01 μS). Consequently, a non-responder describes an individual who fails to show any or a certain (arbitrary) percentage of non-zero CRs. It is of concern that both the definition and treatment (i.e. inclusion vs. exclusion) of non-responders differ widely between studies ('researcher's degree of freedom') (Simmons et al., 2011). Importantly, this is a challenge for comparability of the results across studies, but it may also bias the results due to a potential pre-selection of participants based on individual differences.

Furthermore, 'non-responder' is not a stable trait-like characteristic but is contingent on experimental demands and procedures, and differs between measures (i.e. more frequent in SCRs than in probed FPS) and stimulus types (i.e. more frequent for CS- trials than for CS+ and US trials). As such, using CRs for defining non-responders, likely inter-mixes both physiological non-responses and learning-related non-responses (i.e. lack of contingency awareness). Importantly, this procedure would exclude participants not showing the expected hypothesis-conforming responding, which has to be considered highly problematic. Consequently, we recommend basing the classification of non-responders on zero-responses in unconditioned responding (i.e. physiological non-responders). Alternatively, a series of quick deep breaths and/or forced blinks prior to the experiment or during US calibration may identify physiological non-responders or equipment malfunctioning, and is therefore recommended.

To reduce the 'researcher's degrees of freedom' in this respect, we highly recommend that authors should 1) report the precise criteria used for the classification of zero-responses and non-responders, 2) report a rationale, and 3) report whether the results remain comparable if these exclusion criteria are not applied.

Zero-responses, as described above, have to be distinguished from missing responses due to electrode artefacts, missing button presses, or distorted amplitudes (see 4.1.2.2 and 4.1.1.2). This distinction is important, as missing values do not contribute to the calculation of mean responses or within a repeated-measures analysis of variance, whereas zero-responses do.

Generally, as a convention, the calculation of response *magnitude* includes all zero responses, while response *amplitude* excludes zero responses (Dawson et al., 2007). *Magnitude* inter-mixes response amplitude with response frequency, while the latter is not accounted for in *amplitude* measures. It is recommended that authors should state if magnitude or amplitude are used and indicate the number of zero responses.

4.3.7. Considering temporal dynamics

Responding in fear conditioning is, by definition, temporally dynamic. Accordingly, the time factor should optimally be taken into account. This can be implemented by sub-dividing the experimental phase in smaller time-bins (1st half and 2nd half), including the time factor in statistical analyses, or by implementation of parametric analyses (see 4.1.6.2). For instance, activation in the amygdala, a core area implicated in fear and anxiety possessing, is often only captured in parametric analyses (e.g., Büchel et al., 1998a,b).

Furthermore, mathematical models based on the learning rule proposed by Rescorla and Wagner (Rescorla and Wagner, 1972) can be employed. Briefly, the fear conditioning process is considered a form of predictive learning where expectations are shaped by past experience. Learning does not rely on temporal contiguity (i.e. simply presenting two stimuli together). Instead, an unexpectedly occurring or omitted US leads to a prediction error (denoting the difference between current outcome and prior expectation) that impacts the expected outcome of the next trial. Various extensions and adaptations to this model have been proposed since 1972, that will not be elaborated here (Pearce and Hall, 1980; Sutton and Barto, 1998; Van Hamme and Wasserman, 1994).

Despite their limitations for complex designs (Redish et al., 2007), these dynamic models can be superior to the simple assumption of categorical differences between CS+ and CS-. More precisely, learning models explain more variance in the data, leading to smaller errors in statistical testing, and more importantly, they define the psychological process of learning, and hence provide more thorough interpretations. The implementation of learning models into the analysis is feasible for most experiments and dependent variables (see e.g. 4.1.6.2) even though certain design features may facilitate their implementation. First, continuous sampling within the learning process supports a good model fit as any surprising event (e.g. breaks and ratings) may change the learning curve. Second, consistent temporal aspects (e.g. number of presentations, and time elapsed between first and last presentation) for all stimuli enable similar model fits for all conditions and foster comparability.

5. Methodological considerations for research on individual differences and vulnerable populations

We have previously highlighted that procedural details need to be adapted to the process under investigation. In addition to these general considerations, between-group comparisons targeting individual difference factors or clinical populations require additional considerations. A plethora of individual difference factors influencing fear conditioning processes have been described in the literature (for a review see Lonsdorf & Merz, under review). It is noteworthy that these factors can be of primary interest in studies on individual differences in fear conditioning and hence represent meaningful information themselves. In the context of the present work, targeting general processes of fear learning, individual difference factors however represent noise that should optimally be controlled for in this context (i.e. potentially confounding factors)

An in-depth review and discussion of findings on individual differences in fear conditioning (provided by a separate manuscript of our reserach network; Lonsdorf & Merz, under review) is however beyond the scope of this work, which is tailored to general *methodological considerations* in fear conditioning research. Yet, individual difference factors are of relevance for sample considerations as well as procedural, analytical, and interpretational considerations, which are discussed in detail below. In addition, some of the most important factors are listed in Table 5, to raise awareness on their potential impact on study results even when individual differences are not of primay interest.

5.1. Sample considerations

In studies comparing clinical populations with healthy individuals, an important confounding variable is disorder-specific medication. More precisely, drugs used to treat anxiety, stress-related or affective disorders (e.g. antidepressants or anxiolytics) are known to impact fear conditioning processes and/or specific read-out measures (e.g. Baas et al., 2002; Grillon et al., 2006a,b). Restricting clinical samples to drug-naïve patients will most likely lead to biased sampling as drug intake is generally correlated with symptom and disorder severity. Consequently, reporting medication use and its impact on the results is strongly advised.

Second, matching of cases and controls as well as groups differing by individual difference factors requires special care. As this consideration is not specific to fear conditioning research, we refer to other sources rather than providing an in-depth discussion here (Rose and van der Laan, 2009).

Table 5
Non-exhaustive list of individual difference factors impacting on fear conditioning processes.

Factors	Exemplary references
Age	Gao et al. (2010); Glenn et al. (2012a,b); Labar et al. (2004); Lau et al. (2011); Pattwell et al. (2012); Schiele et al. (2016); for a review see: Shechner et al., 2015
Sex, sex hormones, menstrual cycle and hormonal contraceptives	Glover et al. (2013); Graham and Milad, (2013); Hwang et al. (2015); Inslicht et al. (2013); Lebron-Milad and Milad, (2012); Li and Graham, (2016); Lonsdorf et al. (2015b); Merz et al. (2012, 2013); Milad et al. (2006, 2010); Zeidan et al. (2011), for a review see Cover et al. (2014)
Genetic polymorphisms	Agren et al. (2012); Baas and Heitland (2015); Crisan et al. (2009); Garpenstrand et al. (2001); Glotzbach-Schoon et al. (2013a,b); Hajcak et al. (2009); Hartley et al. (2012); Heitland et al. (2013); Hermann et al. (2012); Wendt et al. (2015); Klucken et al. (2013, 2014); Klumpers et al. (2012); Kuhn et al. (2016); Lonsdorf et al. (2009, 2015a); Mühlberger et al. (2013); Straube et al. (2014); for a review see Lonsdorf and Baas, (2015); Lonsdorf and Kalisch, (2011); Sumner et al. (2015); Torrents-Rodas et al. (2012)
Personality	Arnaudova et al. (2016, 2013); Baas and Heitland, (2015); Barrett and Armony, (2009, 2006); Browning et al. (2015); Chin et al. (2016); Fredrikson and Georgiades, (1992); Gazendam et al. (2015, 2013); Grillon and Ameli, (2001); Haaker et al. (2015); Haddad et al. (2012); Hur et al. (2015); Indovina et al. (2011); Joos et al. (2012); Kindt and Soeter, (2014); Lommen et al. (2010); Morriss et al. (2016a, 2016b, 2015); Otto et al. (2007); Pineles et al. (2009b); Schienle et al. (2010); Sehlmeyer et al. (2011); Torrents-Rodas et al. (2012); for a review see Lonsdorf and Merz (unpublished manuscript)
Brain morphology	Cacciaglia et al. (2014); Hartley et al. (2011); Milad et al. (2007a); Pohlack et al. (2012); Rauch et al. (2005); Winkelmann et al. (2015), for a review see Lonsdorf and Merz (unpublished manuscript)
Mood and affect	Glotzbach-Schoon et al. (2015); Kuhn et al. (2016); Vriends et al. (2011)
Time of day	Pace-Schott et al. (2013)
Stress and cortisol	Antov et al. (2013); Bentz et al. (2013); Hamacher-Dang et al. (2015); Jackson et al. (2006); Merz et al. (2010, 2012, 2014a,b); Raio et al. (2013); Soeter and Kindt (2011a, 2011b); Stark et al. (2006); Stockhorst and Antov, (2015); Tabbert et al. (2010); Zorawski et al. (2006, 2005), for a review see Merz and Wolf (2017)
Sleep	Graves et al. (2003); Marshall et al. (2014); Menz et al. (2013)
Life adversity	McLaughlin et al. (2015); Scharfenort et al. (2016)

Note that these individual difference factors serve as factors of *primary* interest in the study of individual differences in fear conditioning. When intested in the basic principles of fear conditioning however these factors however have the potential to bias and confound results. Hence, authors should be aware of and control for their influences. Note that factors and references related to pathological conditions of any kind (i.e. psychopathology, neurological disorders, and brain lesions) or pharmacological treatment of disorders are not listed.

A third consideration for studies in clinical samples is the impact and role of patient exclusion due to comorbidities (for an in-depth review see Goldstein-Piekarski et al., 2016) and the specificity of the findings to a specific disorder as opposed to sub-types of the disorder. At both a conceptual and practical level, processes that cut across the traditional diagnostic boundaries (e.g. altered fear extinction) rather than diagnostic entities are currently of primary interest, an approach that is in line with the National Institute of Mental Health (NIMH) initiated Research Domain Criteria initiative (Insel et al., 2010).

Finally, when interested in fear conditioning processes in clinical samples, piloting should not be restricted to healthy university students to allow for the identification of specific procedural requirements in the to-be studied sample (e.g. adjustment of trial number due to delayed acquisition and extinction learning in patients).

5.2. Paradigm considerations

Generally, it has been suggested that the potency of the experimental situation may determine the manifestation of individual differences in fear conditioning studies (Lissek et al., 2006). Thereby, *weak* (experimental) situations characterized by complexity, uncertainty, and ambiguity have been suggested to be more sensitive in bringing about individual differences in responding. Strong experimental situations, in turn, are characterized by unambiguity and simplicity, and are expected to induce rather uniform responding across participants (Lissek et al., 2006). Hence, even subtle differences in procedural characteristics that contribute to the potency of the situation (e.g. reinforcement rate, instructions, number of CSs, etc.) may contribute substantially to non-replicability across studies, and therefore, deserve particular attention.

A second procedural consideration in studies on individual differences or clinical populations is the use of experimental stimuli (CS and US) that are related or unrelated to the individual difference factor or the disorder under study. For instance, disorder-specific USs (e.g. pictures/films of feared objects/situations) have been employed in patients with specific phobia (Olatunji, 2006; Schweckendiek et al., 2011) and social anxiety (disorder) (Lissek et al., 2008b; Pejic et al., 2013). The use of both disorder-relevant (see above) as well as – irrelevant USs (social anxiety disorder: Hermann et al., 2002; panic disorder: Lissek et al., 2009; Lueken et al., 2013; specific phobia: Grant et al., 2015; Berntson et al., 2007; Mosig et al., 2014; Vriends et al., 2012) have also been employed. Because of (potentially) stronger reactivity to disorder-relevant stimuli, the interpretation of results might be hampered because associative learning-related effects might not be disentangled from the general impact of US aversiveness/reactivity. To date, studies employing both disorder-relevant and – irrelevant USs in the same sample are rare (for an exception, see for an exception: Schweckendiek et al., 2011). Hence, a meaningful evaluation of differential effects of disorder-relevant versus irrelevant USs in clinical populations cannot yet be provided.

Third, studies investigating fear conditioning-related processes in patients suffering from anxiety disorders may not require a fear acquisition phase when extinction training/exposure treatment or the ROF test directly tackles the specific fear response towards the feared object/context.

Fourth, it has to be acknowledged that specific experimental procedures have been developed to investigate processes relevant to specific clinical populations (e.g., fear vs. anxiety: Davis et al., 2010; social anxiety disorder: Lissek et al., 2008b; intrusions: Wegerer et al., 2013) or to account for specific requirements in other vulnerable populations such as children (Glenn et al., 2012a,b; Lau et al., 2008).

Table 6
Checklist of aspects that are recommended to be specifically mentioned in publications on experimental fear conditioning and reference to the respective subchapter of this manuscript. Accordingly, these aspects comprise judgements to make when designing a fear conditioning study.

Aspects to be mentioned	Subchapter
□ Which CS, US, and context stimuli are used? From which sources are these stimuli derived (e.g. IAPS, self-made)?	2.1.1–3
□ What is the duration of the presentation of the CS, US, context, and ITI in each experimental phase (e.g. 8 s CS, 100 ms US, 3 s context, and 10–12 s ITI in acquisition training)?	2.1.1–4
□ In case of inclusion of a US calibration phase: is the US intensity individually calibrated? If yes, specify the procedure. How many USs are applied to each participant during calibration (average and range)? What is the final intensity of the selected US (average)? In case of a between-group design: are the groups similar regarding self-reported aversiveness and final US intensity? What instructions are provided to the participants with respect to US calibration?	2.1.3, 3.1.
□ What is presented during the ITI (e.g. black screen vs. fixation cross)?	2.1.4
□ Which reinforcement rate is used (e.g. 100% vs. 75%)?	2.2.1
□ How many trials of each stimulus (CS, US, context) are included in each experimental phase (e.g. 4 CS+, CS- during habituation; 12 CS+, 12 CS-, and 8 US in acquisition training; and 12 CS+ and 12 CS- in extinction training)? What is the total duration of each phase (e.g. 10 min acquisition training)?	2.2.2
□ Is the trial order for each experimental phase (pseudo) randomized/counterbalanced across CS/context presentations? If yes, are there any restrictions (e.g. no more than 2 CS+ presentations in a row or no more than 3 presentations of the same contexts in a row)?	2.2.2
□ Which ISI between CS+ onset and US presentation is chosen, and did the presentations overlap (e.g. 7.9 s between CS+ and US, overlapping for the last 100 ms, and co-terminating; i.e. delay conditioning)?	2.2.3
□ What instructions (written and oral) were provided to the participants at any stage of the conditioning protocol (e.g. before habituation, acquisition, or extinction training/test)?	2.2.4
□ Where is the US applied (e.g. right wrist or left toe)? Which endpoint of self-reported aversiveness is used for the US (e.g. 'very unpleasant' or 'unpleasant but not painful') and which criterion (e.g. '7 on a 1–10 scale')?	3.1
□ Is habituation conducted in the same context as the rest of the experimental phases?	3.1.2
□ How are the different experimental phases statistically operationalized and calculated? (e.g. difference CS+ vs. CS- during last block of acquisition vs. during last trial of acquisition for successful acquisition; which trials were included and how was the CS+/CS- difference calculated?)	3.2
□ Report all timing parameters (delay between acquisition and extinction, delay between extinction and ROF/test session, and delay between reinstatement US and test). Are the separate experimental phases conducted in the same or different contexts (e.g. habituation and acquisition training in Context A or extinction training in Context B)?	3.2, 3.4
□ How are transitions between experimental phases (e.g. from acquisition training to extinction training) handled? Are they separated by ratings, instructions, etc., or are performed at different experimental sessions/days?	3.4.1
□ What is presented during application of reinstatement US?	3.5.3
□ Which control condition(s) or group(s) are used to contrast ROF effects, e.g. how is the control condition designed to contrast the reinstatement effects (unpaired USs vs. no USs)?	3.5.4
□ What exact wording is used for questions regarding contingency awareness, US expectancy, and affect ratings, and which answer form is used (e.g. visual analog vs. Likert scale vs. SAM)? At what exact time-points are these questions provided (e.g. before/after the experimental phase or online during/after CS presentation)?	4.1.1–2
□ In case of SCR analyses: Are between-group comparisons for CRs and URs included (raw and transformed values)?	4.2.1.2
□ When applying transformations to data (e.g. Z or T) or corrections (e.g. range-correction): which data points are included, and are transformations applied across all experimental phases or are done so separately for each experimental phase/day?	4.2.1.3, 4.3.6
□ In case the specific research question requires performance-based exclusion of participants: what are the precise criteria used for this definition (including the number of trials and outcome measure the value is based on)? What is the rationale for this approach? Do the reported results remain comparable if these exclusion criteria are not applied (i.e. a sensitivity analysis)?	4.3.2
□ Which precise criteria are used for the classification of zero-responses and/or non-responders? What is the rationale for this approach? How are non-responses handled during data analyses (e.g. exclusion of non-responders or using the non-response rate as a covariate)? Do the reported results remain comparable if these exclusion criteria were not applied?	4.3.4
□ Are there missing responses due to electrode artefacts, missing button presses, or distorted amplitudes separately from zero-responses?	4.3.4
□ Always report the sociodemographic data for the participants included in the final analyses (if necessary for all subsamples, e.g. in multiple day paradigms or for different measures).	4.3.6
□ In case of multiple day paradigms: has the US intensity been re-calibrated individually only prior to fear acquisition or prior to every experimental session? How are potentially variable external (e.g. electrode placement or time of day) or internal (e.g. sleep-, hormone-, or mood-related) variables controlled for or handled?	4.3.6
□ Are there CS-specific results in addition to group differences in CS-discrimination (e.g. group differences in CS+/CS- differentiation may be traced back to differences in responding to the CS-)?	4.3.6
□ Report possible confounding factors and how they are controlled for or handled.	5.1
□ In case of clinical samples: report (disorder-specific) medication use and its influence on the results. Report comorbidities and disorder-subtypes of patients. Which variables (e.g. age and sex) does the matching procedure between patients and controls encompass?	5.1

5.3. Analysis and interpretational considerations

When statistically comparing CRs during fear acquisition training, extinction training, and the ROF test between groups, several challenges need to be considered. First, patients as well as highly anxious individuals (Baas et al., 2008; Chan and Lovibond, 1996; Grillon, 2002b) and controls commonly differ in verbal reports of contingency awareness (see 4.2.1), which may also manifest in group differences in post-acquisition responding. Hence, in studies reporting between-group comparisons, it is particularly critical to include reports of results from all experimental phases despite a specific theoretical interest in a later experimental phase. In absence of such a comprehensive description of group differences, an adequate interpretation of the data is not possible.

Second, several considerations with respect to group comparisons mentioned in previous sections have to be referred to as they are particularly relevant for between-group comparisons. This includes the assessment of unconditioned responding, range-correction of data (see 4.1.1.3), and performance-based exclusion of participants (see 4.3.4 and 4.3.6), as well correction for preceding within-session performance (see 4.3.5).

Third, phenotypes for the study of individual difference factors need to be quantified reliably and reproducibly over time (i.e. *test-retest reliability*). Within-subject reproducibility and test-retest reliability in fear conditioning research has been established for conditioned SCRs across time intervals ranging from three weeks to eight months (3 weeks: Fredrikson et al., 1993; 8 months: Torrents-Rodas et al., 2014; 8–12 weeks: Zeidan et al., 2012) with intermediate reliability coefficients. Furthermore, temporal stability has also been reported for differential conditioned startle responding as well as 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) and CS- responding (SCRs: Fredrikson et al., 1993) as well as CS+/CS- discrimination during fear acquisition (SCRs, FPS and US expectancy: Torrents-Rodas et al., (2014); SCRs: Zeidan et al., 2012), extinction recall and renewal (first two trials each in SCRs: Zeidan et al., 2012), and fear generalization (SCRs, FPS, US expectancy: Torrents-Rodas et al., 2014). Importantly, extinction responding (last two trials), in turn, did not display significant test-retest reliability (SCRs: Zeidan et al., 2012), which might be explained by floor level responding. Notably, these findings are based on multiple fear conditioning sessions employing identical (Fredrikson et al., 1993; Torrents-Rodas et al., 2014; Zeidan et al., 2012) or different experimental stimuli (Torrents-Rodas et al., 2014) across sessions, with the former showing somewhat compromised stability. Of note however, higher-level cognitive learning processes (that are unavoidable when a paradigm involving a learning element is repeated) likely affect test-retest reliability coefficients. For instance, in an acquisition-extinction protocol, participants learn at T1 that USs are presented in the beginning of the experiment but are not given during a later phase. This knowledge is likely to speed up extinction during a repetition of the same protocol later (T2).

6. Conclusions and outlook

This methodological compendium, which represents a joint effort of representatives from fourteen major European laboratories in the field of fear conditioning research, is intended to serve as a basis for a common procedural framework for the field of human fear conditioning and provide guidance for methodological decisions on design and analysis. Furthermore, to foster comparability and interpretation of findings across different publications, we provide a check-list that is based on this review and that lists methodological aspects that should be mentioned in publications in the field in the future (see Table 6) Originating from the zeitgeist of the 'replicability crisis' in science and psychology in general, we hope to ultimately establish consensus in the field with respect to design and analysis considerations by raising awareness regarding and critically discussing important methodological considerations in the field of fear conditioning. Despite this overarching aim, procedural details clearly cannot be unified in the minutest details as procedures necessarily have to be tailored to the specific research question. Hence, the guidelines provided here should by no means restrict the development of innovative and novel approaches that elaborate upon what we have learned during the past decades.

Yet, we hope that our work will lift the field towards a level of enhanced replicability and methodological as well as interpretational transparency (reducing 'researcher's degree of freedom'). In addition, we hope to spark fruitful discussions and (cross-laboratory) methodological research projects to aid the development of the field.

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