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Avoidance and its bi-directional relationship with conditioned fear: Mechanisms, moderators, and clinical implications

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ABSTRACT

Fear motivates different types of defensive behaviors. These behaviors are, however, not mere byproducts of fear. In this review, we highlight a bi-directional relationship between conditioned fear and instrumental defensive behavior in humans. We discuss mechanisms involved in the link from fear to goal-directed avoidance (e.g., relief, generalization), that may become habitual. These defensive behaviors may in turn reduce, preserve, or amplify fear responding (e.g., protection-from-extinction, behavior-as-information). Multiple factors moderate the bi-directional relationship. Evidence for amplifying and dampening effects of inter-individual differences (e.g., trait anxiety, distress tolerance), intra-individual states (e.g., stress), and external factors (e.g., incentives for competing behavior) on goal-directed and/or habitual defensive behavior is reviewed. However, the exact mechanisms by which these factors moderate the bi-directional relationship are still largely unknown (e.g., modulating avoidance directly vs. indirectly via conditioned fear). Finally, we discuss major implications: First, understanding factors moderating the bi-directional relationship provides insights into risk and resilience factors for anxious psychopathology. Second, specific experimental models and clinical interventions can be mapped onto distinct defensive behaviors (e.g., goal-directed vs. habitual avoidance). More precise matching will help to develop nuanced models and interventions to reduce pathological behaviors and individualize treatments.

1. Introduction

Defensive behaviors can be defined as behavioral responses to threat and harm (LeDoux & Daw, 2018). These behaviors are adaptive to prevent realistic threat and harm. However, defensive behaviors which are persistent and out of proportion to the actual threat are maladaptive and a key feature of anxious psychopathology. Although defensive behaviors are motivated by fear, they are not simple byproducts of fear learning and recent evidence suggests that defensive behaviors also affect conditioned fear. This review focuses on the relationship between conditioned fear and different types of defensive behaviors (i.e., defensive reactions, goal-directed defensive actions, and defensive habits). The main goals are to 1) discuss mechanisms of instrumental defensive behavior and its bi-directional relationship with conditioned fear, 2) discuss factors moderating this relationship, and 3) discuss implications for experimental psychopathology and clinical interventions. For this purpose, the review mostly focuses on human aversive conditioning research.

More than 100 years of human aversive conditioning research highlight a long and successful tradition of using a reductionistic, highly controlled experimental procedure of human aversive learning. Substantial progress was made in understanding the mechanisms and moderators underlying Pavlovian fear acquisition, generalization, extinction, and the return of conditioned fear as well as their contributions to anxiety and related disorders (e.g., Craske et al., 2017; Dunsmoor & Paz, 2015; Lonsdorf & Merz, 2017; Mineka & Zinbarg, 2006; Pittig, Treanor, LeBeau, & Craske, 2018; Pittig, van den Berg, & Vervliet, 2016; Shechner, Hong, Britton, Pine, & Fox, 2014; Vervliet, Baeyens, van den Bergh, & Hermans, 2013). Pavlovian fear acquisition represents the formation of an association between a formerly neutral conditioned stimulus, also referred to as the CS+ or warning signal, and an aversive unconditioned stimulus (US, e.g., aversive electrical

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stimulation or loud noise).[1] The acquired CS-US association enables humans to predict aversive events, which is an adaptive process to prevent harm. However, a CS-US association itself is not sufficient for preventing or coping with harm and danger. To this end, the CS-US association needs to be translated into defensive behavior.

In humans, successful acquisition of conditioned fear is expressed in subjective-cognitive responses (e.g., verbal reports of threat expectancies or feelings of fear), physiological changes (e.g., skin conductance responses, neural changes), and behavioral responses (Lonsdorf, Menz, Andreatta, Fullana, Golkar, Haaker and Merz, 2017). Using behavioral responses to infer about fear learning was already evident in the early “Little Albert” study (Watson & Rayner, 1920). Albert's ducking, bending, or crawling away from a rat were used as major indicators for assuming that fear was acquired after pairing the rat with a loud noise. However, fear learning and its expression are two different processes, which interact, but cannot be inferred from each other in an axiomatic manner. In rats, Tolman and Honzik (1930), for example, demonstrated that learning can occur without changes in behavior (*latent learning*). A lack of behavioral responses thus does not necessarily indicate a lack of learning. Moreover, Pavlovian learning is not necessarily expressed in overt behaviors as multiple factors apart from fear learning determine the expression of a specific behavior. The same is true for self-reported and physiological indicators of fear, which helps to explain why different indicators oftentimes do not converge (see Lonsdorf et al., 2017). This review does not aim to discuss the association between different levels of fear expression (subjective, physiological, behavioral), but the impact of conditioned fear, as established by Pavlovian fear acquisition training, on the expression of defensive behaviors and vice versa.

The differentiation between learning and behavior is further complicated when different types of behaviors are lumped together, ignoring differences concerning their effects, complexities, underlying learning processes, and how closely they are linked to Pavlovian conditioned fear. Based on recent taxonomies (see Krypotos, Vervliet, & Engelhard, 2018; LeDoux & Daw, 2018), we therefore provide some considerations about different types of defensive behaviors and their links to maladaptive behaviors in clinical populations (see Table 1 & Fig. 1).

1.1. *Defensive reactions, goal-directed defensive actions, and defensive habits*

Defensive behaviors can be separated into defensive reactions, goal-directed defensive actions, and defensive habits[2] (LeDoux & Daw, 2018; Mobbs, 2018; Pittig, Treanor et al., 2018; see also the foundation in appetitive behavior, e.g. Balleine & Dickinson, 1998; Dickinson, 1985). *Defensive reactions* are innate reflexive reactions, i.e., they are automatically elicited by a preceding stimulus (LeDoux & Daw, 2018). An example is the human startle reflex as an overt response to a sudden loud noise. These defensive reactions are assumed to be relatively hardwired behaviors, which are not learned themselves. Nevertheless, their expression can be modulated by acquired Pavlovian stimuli. One of the first examples of a conditioned defensive reaction is the “conditioned leg reflex” to lights that were previously paired with electrical stimulations to one foot (see Bekhterev, 1913, which later influenced Watson & Rayner, 1920). Similarly, fear-potentiated modulation of the

Table 1
Suggested terms for different defensive behaviors.

Conditioning term	Clinical term	Definition	Laboratory example	Clinical example
CS-avoidance	Avoidance	CS is avoided	Choosing an options that prevents CS presentation and thereby prevents US	Staying away from the inner city to avoid shopping malls
US-avoidance	Safety behavior	US is avoided while CS is not terminated	Button press during CS which prevents US, but does not terminate CS	Participate in social event, only speak after mentally rehearsing
CS-escape	Threat escape	CS is terminated and thereby US avoided	Button press during CS which terminates CS and prevents US	Escape from bus after boarding
US-escape	Harm escape	US is terminated	Button press during US presentation which terminates US	Leaving insulting social interaction

Note. Based on Krypotos et al. (2018). CS = Conditioned stimulus. US = aversive unconditioned stimulus.

[1] While some proponents view this CS-US association as an automatic excitatory link (e.g., Bouton, 2007; Mclaren, Green, & Mackintosh, 1994), other proponents see this association as a propositional representation (e.g., De Houwer, 2011; Mitchell et al., 2009). Since we do not attempt to reconcile these two theoretical views, we will simply refer to the relationship between the CS and the US as CS-US association in the current review.

[2] In this regard, fight or aggressive behavior can also constitutes a defensive behavior, which is, however, not discussed in this review.

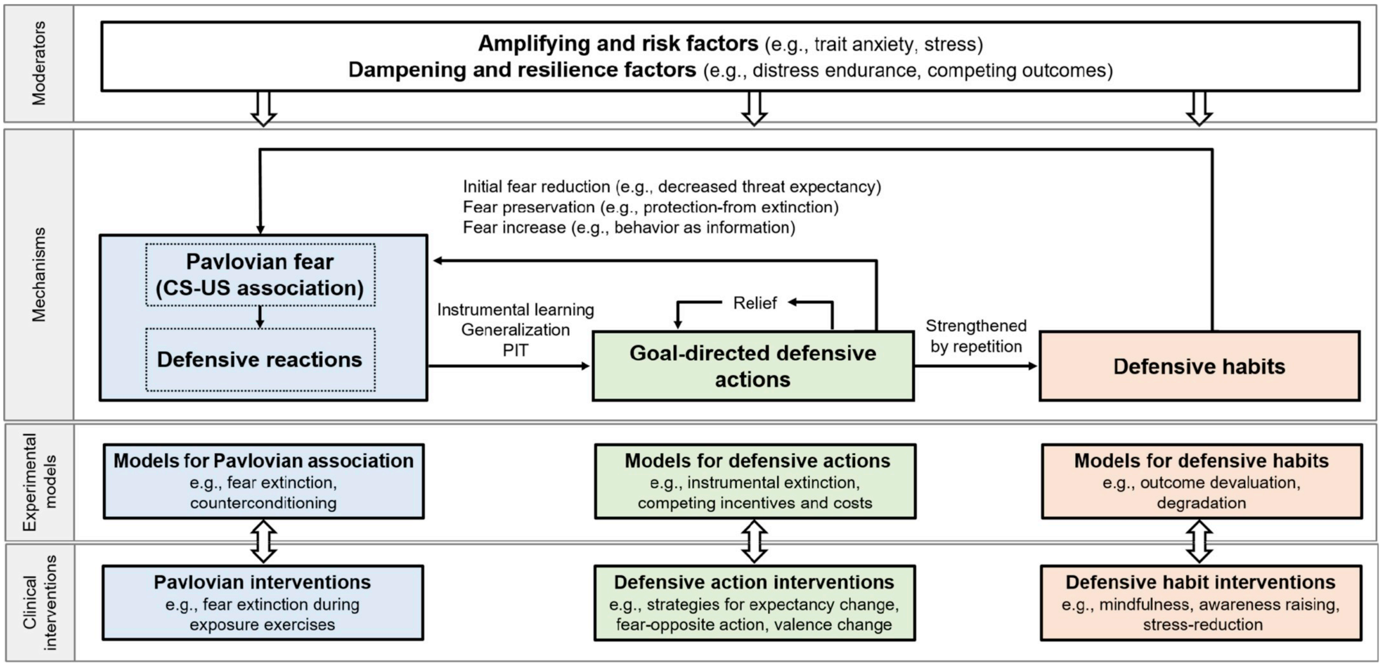

Fig. 1. The bi-directional relationship between human Pavlovian fear and defensive behaviors, moderators for this relationship, and the mapping of experimental models and clinical interventions onto distinct defensive behaviors. Moderators may directly modulate conditioned fear, instrumental defensive behavior, and/or one or both directions of the link between fear and instrumental defensive behavior. Goal-directed defensive actions arise from Pavlovian conditioned fear via instrumental learning processes. The degree of defensive actions is further influenced other processes such as fear generalization, Pavlovian-to-instrumental transfer, or relief processes. Repetition of goal-directed defensive actions leads to a transition from defensive actions to more habitual defensive behaviors. Both defensive actions and habits can attenuate (i.e., initial fear reduction) or amplify conditioned fear (i.e., fear preservation and/or fear increase).

startle eye-blink during presentation of a fear-conditioned CS has more recently been demonstrated in humans (e.g. Grillon, Ameli, Woods, Merikangas, & Davis, 1991; Lissek et al., 2008). Defensive reactions in response to a CS + can also be reduced through Pavlovian interventions such as Pavlovian fear extinction (see Fig. 1). Fear extinction involves repeated presentations of the CS+ in absence of an US. According to the inhibitory learning theory, fear extinction training establishes a novel CS-NoUS association which inhibits the expression of the original CS-US association (e.g. Craske et al., 2008; Milad & Quirk, 2012; Quirk & Mueller, 2008). Recent reviews provide excellent discussion of defensive reactions (e.g., Cain, 2019; LeDoux & Daw, 2018). Additionally, broader overviews on Pavlovian fear acquisition and extinction, the impact of individual differences, and clinical implications also include insights about defensive reactions such as the fear-potentiated startle reaction (e.g., Craske, Hermans, & Vervliet, 2018; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Lonsdorf & Merz, 2017; Merz, Kinner, & Wolf, 2018; Pittig et al., 2016; Pittig, Treanor et al., 2018; Shechner et al., 2014). Therefore, we will not focus on defensive reactions in this review, but on two other types of defensive behaviors: goal-directed defensive actions and defensive habits. As both types are acquired via instrumental learning, we will refer to them as *instrumental defensive behaviors*.

Goal-directed defensive actions are instrumental behaviors that are determined by their expected outcomes, the current motivational value of the outcomes, and the association between performance of an action and the actual occurrence of an outcome (response-outcome (R–O) contingency). Goal-directed actions are typically more elaborate, elicited more slowly, and can take more arbitrary forms than defensive reactions (e.g., pressing a button), i.e., they are not limited to an innate set of reactions and reflexes (see Balleine & Dickinson, 1998; Strack & Deutsch, 2004; but also see Moors, Boddez, & De Houwer, 2017). The signaled active avoidance paradigm employed in human aversive conditioning research is a typical example of a goal-directed defensive action. In this paradigm, actively performing an experimenter-defined response (e.g., button press) during presentation of the CS + prevents

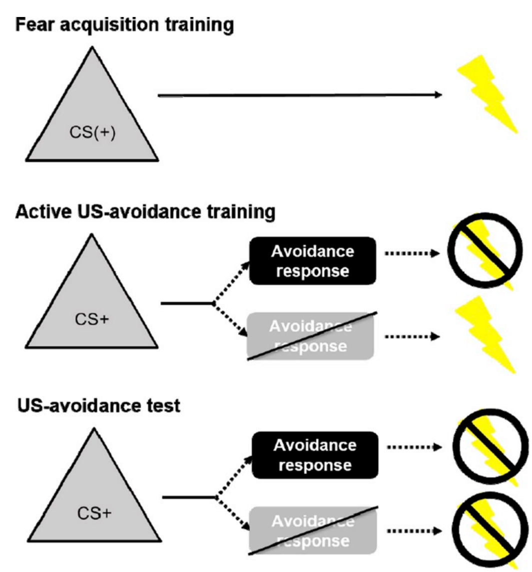

Fig. 2. Graphical depiction of a typical human US-avoidance paradigm. During fear acquisition training, the Pavlovian CS-US association is acquired by repeated pairing of a CS with an aversive unconditioned stimulus (e.g., unpleasant electrical stimulation). During the active US-avoidance training, participants learn that they can prevent the aversive US by performing a designated avoidance response (e.g., button press). If the response is not performed, the CS is followed by the US. A subsequent test phase is often conducted in absence of the US, irrespective of the avoidance response being performed or not.

occurrence of the aversive US, but does not terminate the CS+ (see Fig. 2). In this paradigm, the relevant outcome following defensive actions is the occurrence vs. non-occurrence of the US (see US-avoidance below). In addition, the CS + may be a relevant outcome for defensive actions. Pavlovian fear acquisition training also entails evaluative learning by which the CS + obtains a negative valence, meaning that it is increasingly perceived as unpleasant itself (Baeyens, Field, & De Houwer, 2005; Hermans et al., 2005; Hermans, Spruyt, & Eelen, 2003; Hermans, Vansteenwegen, Crombez, Baeyens, & Eelen, 2002). This unpleasantness may activate automatic avoidance tendencies in presence of the CS+ (e.g., Chen & Bargh, 1999; Krypotos, Effting, Arnaudova, Kindt, & Beckers, 2014). Moreover, the CS + can become a second-order negative outcome which triggers defensive actions to avoid the CS + itself (i.e., CS-avoidance; Pittig, Schulz, Craske, & Alpers, 2014). In a clinical context, goal-directed defensive actions can thus be changed through interventions that target the expected outcomes (e.g., behavioral and cognitive strategies for expectancy change) or change the negative valence of the CS+. As conditioned fear is only one factor influencing goal-directed action, expected outcomes, their values, and the action-outcome contingency can be modulated by multiple interventions such as establishing competing outcomes to initiate fear-opposite action (see Fig. 1). We further elaborate on these strategies in the clinical implications.

Goal-directed actions can become habitual due to overtraining (see Fig. 1). *Habitual defensive responses* are thus also controlled by instrumental learning processes (Balleine & Dickinson, 1998; Balleine & O'Doherty, 2010; Dickinson, 1985). Similar to defensive reactions, habitual responses are elicited quickly by preceding stimuli and are automatic, reflexive responses. Unlike defensive reactions, habitual responses can take completely arbitrary forms (e.g., button pressing), because they are always instrumentally learned. In contrast to goal-directed actions, defensive habits are not controlled by their outcomes anymore and are independent from changes in their outcomes. Habits are thus relatively insensitive to the devaluation of their outcome and to the degradation of action-outcome contingencies (see Balleine & O'Doherty, 2010; Dayan & Niv, 2008; Dolan & Dayan, 2013; Wood & Rünger, 2016; but see also De Houwer, Tanaka, Moors, & Tibboel, 2018; Moors et al., 2017). The development of habits may help to explain why defensive behaviors persist after fear extinction (Arnaudova, Kindt, Fanselow, & Beckers, 2017; LeDoux & Daw, 2018; LeDoux, Moscarello, Sears, & Campese, 2017). Thus, the interaction between goal-directed and habitual processes seems to play a role in controlling the learning and expression of instrumental defensive behavior (Dayan & Niv, 2008). Clinically, habitual defensive responses should be relatively resistant to interventions targeting outcomes, thus requiring distinct interventions (see Fig. 1).

1.2. Escape, avoidance, and safety behavior

Besides distinguishing between reactions, actions, and habits, defensive behaviors can also be differentiated based on their effects (see Table 1; see also Krypotos et al., 2018). In this regard, escape and avoidance are qualitatively different. Escape responses terminate the presentation of or increase the tempospatial distance to either a threatening stimulus (*threat escape*) or ongoing harm (*harm escape*). In human aversive conditioning, threat escape is typically operationalized as responses that terminate the CS (i.e., CS-escape) and harm escape as responses that terminate an ongoing US (i.e., US-escape). Avoidance responses, in contrast, do not terminate, but completely prevent the presentation of either a threatening stimulus or harm. Avoidance can be active or passive, depending on whether a response needs to be performed (active avoidance) or inhibited (passive avoidance).

In addition, avoidance can be directed to the CS (CS-avoidance) or the US (US-avoidance). Active US-avoidance, as depicted in Fig. 2, involves performance of an avoidance response during CS presentation to effectively prevent the US. In contrast, CS-avoidance prevents presentation of the CS and consequently the occurrence of the US. Both US-avoidance and CS-avoidance are typically referred to as "avoidance" in experimental research. In clinical contexts, they are more strictly separated. The term "avoidance behavior" typically refers to the complete avoidance of a feared stimulus or an anxiety-related situation (i.e., CS-avoidance), e.g., when an individual with social anxiety completely avoids social events. In contrast, "safety behavior" refers to behaviors where the stimulus or situation is approached and endured while concomitantly, behaviors are performed to prevent harm (i.e., US-avoidance), e.g., engaging in a conversation at a social event only after dialogues have been mentally rehearsed. Although both CS- and US-avoidance are of high relevance in the clinical context, most human aversive conditioning research examined US-avoidance. CS-avoidance has only been investigated in few studies (e.g., Pittig & Dehler, 2019; Pittig, Schulz et al., 2014). Overall, better distinguishing between defensive behaviors by means of their effects may add clarity to the communication between basic and clinical research.[3]

1.3. The bi-directional relationship and its moderators

So far, we highlighted the impact of conditioned fear on subsequent defensive behaviors. As displayed in Fig. 1, conditioned fear and instrumental defensive behavior influence each other in a bi-directional manner: Conditioned fear may result in subsequent instrumental defensive behaviors which in turn modulates conditioned fear in multiple ways. Initially, effective instrumental defensive behaviors can reduce fear responding. Importantly, these behaviors can also have a long-term effect on acquired fear. For example, persistent instrumental defensive behavior preserves fear responding and threat beliefs in the absence of threat (i.e., protection from extinction, see Lovibond, Mitchell, Minard, Brady, & Menzies, 2009; Pittig, 2019) or may even increase fear responding to safety stimuli (Engelhard, van Uijen, van Seters, & Velu, 2015). In the clinical context, this bi-directional relationship has long been recognized to produce a vicious circle of fear and avoidance, as well as a conflict between short- and long-term consequences of avoidance (i.e., short-term fear reduction vs. long-term preservation of fear and impairments, see Lang & Helbig-Lang, 2012). Although research is still scarce, we will discuss potential mechanisms of how instrumental defensive behaviors may affect conditioned fear.

Taken together, humans can acquire different types of defensive behaviors via Pavlovian, goal-directed, and habit learning. Additionally, avoidance and escape behaviors can be further split up regarding whether they relate to USs or CSs. With regard to experimental psychopathology and psychotherapy research, a careful differentiation between these different types of defensive behaviors is important in two ways. First, it allows for a more precise investigation how these specific types of defensive behaviors are learned and expressed, how they differentially affect conditioned fear, and which factors may modulate these processes (see Fig. 1, Moderators). Instrumental defensive behaviors are not an inevitable consequence of conditioned fear. While some individuals develop persistent fear-driven avoidance following an aversive experience, others will confront feared stimuli and situations. Understanding factors that moderate the degree of instrumental defensive behaviors following fear learning may help to understand why some individuals do develop anxious psychopathology while others do not (Mineka & Sutton, 2006; Rachman, 1990). Clinically, understanding these moderating factors may improve the identification of risk and resilience factors and ultimately informs prevention approaches for anxiety and related disorders. Second, the distinction between different types of defensive behaviors as well as their underlying learning processes can be mapped onto different experimental models and clinical interventions targeting these processes. In the framework of experimental psychotherapy, this may ultimately inform corresponding clinical interventions to improve treatment of

[3] Although experiential avoidance, another type of clinical avoidance defined as an avoidance of internal negative thoughts and feelings (e.g., Hayes, Wilson, Gifford, Follette, and Strosahl, 1996) is also of clinical importance, it falls outside the scope of the current review.

anxiety and related disorders (see Fig. 1. Experimental models & Clinical interventions).

We will discuss potential mechanisms for the link between conditioned fear and instrumental defensive behaviors as well as moderators for both directions of this link. Some of the proposed moderators are based on theoretical reasoning with yet little empirical evidence. We highlight these potential moderators in hope to inspire future research. In addition, the list of moderators is not meant to be exhaustive. We will mostly focus on active goal-directed US-avoidance as it is most commonly investigated in the field of human aversive conditioning (however, other types such as CS-avoidance may have equal or higher clinical relevance; see Future directions). For the sake of readability, we will use the term 'goal-directed avoidance' when referring to active goal-directed US-avoidance and specify whenever other types of defensive actions are discussed (e.g., active goal-directed CS-avoidance). We will also discuss the contribution of defensive habits, although research is still scarce. We will refer to active habitual US-avoidance as 'habitual avoidance' and specify other types of habits. In concern of the length of the review, we refer to other recent reviews on the neural correlates of defensive behaviors (see Cain, 2019; LeDoux & Daw, 2018; Mobbs, Hagan, Dalgleish, Silston, & Prévost, 2015).

2. Mechanisms in a bi-directional relationship

2.1. From conditioned fear to instrumental defensive behaviors

A considerable amount of studies incorporating low-cost goal-directed avoidance provide evidence that newly acquired fear-conditioned stimuli motivate instrumental defensive behaviors in humans. For instance, participants were more likely to perform a designated avoidance response to a CS + than to a conditioned safety signal (CS-; e.g., Boyle, Roche, Dymond, & Hermans, 2016; Dymond, Schlund, Roche, & Whelan, 2014; Vervliet & Indekeu, 2015). Most theories on human avoidance learning integrate Pavlovian and instrumental learning processes to explain the development of instrumental defensive behaviors. Initially, the two-factor theory proposed that fear reduction following CS termination was the major reinforcer of defensive actions (Mowrer, 1951, 1960). There is now compelling evidence that the non-occurrence of the aversive event (US omission), CS termination, or the occurrence of safety signals indicating successful US-avoidance can all function as reinforcers of defensive actions (for an overview see Cain, 2019; Krypotos, Effting, Kindt, & Beckers, 2015; LeDoux, Moscarello, Sears, Campese, & V, 2017).

The underlying instrumental learning process depends on several factors. The most prominent instrumental factors are the expected outcome and its current motivational value and knowledge about the contingency between action and outcome (e.g. Balleine & Dickinson, 1998; Dickinson & Balleine, 1994). In human aversive conditioning, the motivational value of the outcome is assumed to be inherent to the paradigm as an individual prefers not experiencing an aversive US. Knowledge about action-outcome contingencies can be instrumentally acquired through direct experience by means of trial and error: individuals learn on a trial-to-trial basis that performing or not performing an action in the presence of the CS + determines whether the aversive outcome does or does not occur. At least in humans, additional learning pathways exist. For example, verbal instruction or observation suffice to establish action-outcome contingencies (e.g., Cameron, Roche, Schlund, & Dymond, 2016). Humans can also forecast novel action-outcome contingencies by inferring them from earlier experiences (e.g., Dymond et al., 2011). In humans, it can thus be assumed that goal-directed defensive actions are mediated by the expectancy that the US will be prevented when performing a defensive action and the expectancy that the US will occur when not performing the action (Lovibond, 2006; Seligman & Johnston, 1973). As the CS + obtains a negative valence or unpleasantness, it acquires a motivational value itself. Consequently, the CS may activate automatic avoidance tendencies (e.g., M. Chen & Bargh, 1999; Krypotos et al., 2014) and function as a second-order negative outcome, which can result in defensive actions that aim at avoiding the respective CS (e.g., Pittig, Schulz et al., 2014). Similarly to US-avoidance, this goal-directed CS-avoidance can then be mediated by the current motivational value of the CS and the expectancy to effectively prevent the occurrence of the CS.

Recent research on relief responses seeks to explain the instrumental learning process in more detail. Moreover, defensive actions may not only be performed to the original CS+, but also in response to novel stimuli that resemble the CS+ (generalization). Furthermore, goal-directed defensive actions, which have previously been acquired in absence of a CS (e.g., unsignaled avoidance), can be facilitated in the presence of a CS+. This conditioned facilitation is one part of the so-called Pavlovian-to-instrumental transfer (PIT) effect. In addition to the processes highlighted above, we will discuss how relief, fear generalization, and Pavlovian-to-instrumental transfer may determine the degree of goal-directed avoidance.

2.1.1. Relief

Relief refers to a positive affective state an individual experiences when an expected negative event is omitted (Roseman, 1996; Roseman, Spindel, & Jose, 1990). Evidence also showed that a signal that indicates the termination of an US triggers relief. For instance, humans showed EMG startle attenuation to the CS in a backward conditioning procedure where the aversive US was followed by a CS, a pattern seen as relief learning (Andreatta, Mühlberger, Yarali, Gerber, & Pauli, 2010). On a neural level, the activation of the ventral striatum in humans and the nucleus accumbens in rats are required to express relief learning to the CS (e.g., Andreatta et al., 2012; Mohammadi, Bergado-Acosta, & Fendt, 2014; Mohammadi & Fendt, 2015). These findings suggest that when the temporal positions of the CS and the US are reversed, the CS no longer signals threat of the US. Instead, it signals the termination of the US and thereby elicits a relief response. Given that the ventral striatum-nucleus accumbens circuit is responsible for appetitive prediction error processing (Gerber et al., 2014; Scott et al., 2007; Seymour et al., 2005), the activation of this neural circuit during relief learning suggests that relief can be seen as appetitive learning.

Similar to Pavlovian conditioning, Oleson, Gentry, Chioma, and Cheer (2012) found that when goal-directed avoidance during CS + presentation prevented an upcoming US, a subsequent release of dopamine in the nucleus accumbens was observed in rodents. The release of dopamine in the nucleus accumbens in response to avoidance behavior that effectively prevents the US is seen as a neural mechanism underlying relief learning (Ilango, Shumake, Wetzel, Scheich, & Ohl, 2012). Furthermore, the release of dopamine resembles reinforcement learning signals during reward administration in appetitive conditioning, which implies that the release of dopamine can be seen as reinforcing goal-directed avoidance (Darvas, Fadok, & Palmiter, 2011; Gentry, Lee, & Roesch, 2016; Oleson & Cheer, 2013). In other words, relief learning is one potential underlying mechanism that reinforces goal-directed avoidance. To our knowledge, only one study examined the interplay between goal-directed avoidance and relief learning in human aversive conditioning. Vervliet, Lange, and Milad (2017) found that participants showed increased self-reported relief ratings and skin conductance responses after having avoided an US, comparable to relief ratings to a conditioned safety stimulus. This supports the notion that relief after US omission reinforces goal-directed avoidance. Furthermore, US expectancies were also found to correlate positively with self-reported relief ratings (Vervliet et al., 2017). This suggests that the degree of threat expectancy may mediate the magnitude of relief upon US omission, which speculatively reinforces goal-directed avoidance. However, more evidence is required to examine whether goal-directed avoidance per se can trigger relief learning, or is at least mediated by US omission caused by goal-directed avoidance.

2.1.2. Generalization

Once fear is acquired, it can spread to novel stimuli or situations that resemble the original stimulus or situation. This phenomenon is called fear generalization. Studies on fear generalization in humans conventionally examined how fear generalizes on a perceptual dimension (perceptual generalization; e.g., Dunsmoor, Mitroff, & LaBar, 2009; Lissek et al., 2008; Torrents-Rodas et al., 2013). In a typical perceptual generalization study, novel stimuli resembling the original CS+ to different degrees are presented after fear acquisition training (e.g., novel tones that differ in frequency to the CS+). As a result, the magnitude of fear responses is a function of the degree of physical similarity between CS+ and the novel generalization stimuli (GSs). In other words, less conditioned fear is shown to novel GSs that are less perceptually similar to the CS+ (i.e., generalization decrement; Baron, 1973; Cross & Lane, 1962; Laberge, 1961; Thomas, Mood, Morrison, & Wiertelak, 1991; Wong & Lovibond, 2017).

Recently, Van Meurs, Wiggert, Wicker, and Lissek (2014) examined the generalization of fear-driven goal-directed avoidance by combining Pavlovian and instrumental conditioning. As expected, generalization decrement was observed in both self-reported threat expectancies and startle responses in the Pavlovian generalization phase. In the instrumental generalization phase, goal-directed avoidance to the GSs showed a similar pattern: avoidance was more frequent for GSs with higher similarity to the CS+. Moreover, the generalization gradient of startle responses was positively associated with the generalization gradient of goal-directed avoidance, suggesting a link between the generalization of fear and goal-directed avoidance. Similar patterns were also found in more recent studies (Arnaudova, Krypotos, Effting, Kindt, & Beckers, 2017; Cameron, Schlund, & Dymond, 2015; Hunt, Cooper, Hartnell, & Lissek, 2019). Combined, these studies suggest that perceptual generalization of fear is one mechanism determining the degree of goal-directed avoidance to stimuli that resemble the original fear stimulus.

More recent studies also examined other fear generalization processes, for example, generalization to stimuli that conceptually resemble the CS+ (conceptual generalization; e.g., Bennett, Vervoort, Boddez, Hermans, & Baeyens, 2015; Dunsmoor & Murphy, 2014; Vervoort, Vervliet, Bennett, & Baeyens, 2014). For instance, Boyle et al. (2016) found that participants showed more avoidance to a GS (e.g., the word "soup") semantically related to the CS+ (e.g., "broth") than to another GS (e.g., "help") semantically related to the CS- (e.g., "assist"). Moreover, we recently showed that participants showed more costly GS-avoidance (i.e., responses preventing the presentation of GSs despite costs) to GSs that belonged to the same category as the CS+ (e.g., animals; Wong & Pittig, accepted). Similarly, GSs that shared the same artificial category with the CS+ triggered greater goal-directed avoidance than GSs that belonged to the artificial CS- category (symbolic generalization; Augustson & Dougher, 1997; Dymond et al., 2011; Dymond et al., 2014; Dymond, Roche, Forsyth, Whelan, & Rhoden, 2007). In addition to perceptual generalization, conceptual generalization can thus determine the degree of goal-directed avoidance.

2.1.3. Habit learning

Repetitively performed goal-directed avoidance responses may turn into defensive habits (see Fig. 1; Arnaudova, Kindt et al., 2017; LeDoux et al., 2017; LeDoux & Daw, 2018; Pittig, Treanor et al., 2018). The differentiation between goal-directed and habitual responses takes into account that instrumental learning in signaled active avoidance paradigms includes the relationship between three components: a stimulus (S, the CS+), a response (R, avoidance response), and an outcome (O, US omission). As described above, goal-directed actions are controlled by action-outcome contingencies, i.e., the association between response and outcome (R–O). In contrast, habitual responses are independent of their outcomes. Instead, they are controlled by the learned stimulus-response association (S-R), i.e., the association between the CS+ and the defensive response. Although habitual learning already seems to develop during early avoidance acquisition training, goal-directed processes dominate behavioral expression in these early training stages (Zwosta, Ruge, Goschke, & Wolfensteller, 2018). However, the balance between goal-directed and habitual processes has been found to shift towards habitual processes with prolonged instrumental training (Balleine & O'Doherty, 2010). Specifically, participants initially learn that an avoidance response results in the desired outcome of US omission whenever a CS+ is presented (S-R-O). With repetition, the association between CS+ and avoidance response (S-R) is strengthened until the CS+ habitually triggers the response. Goal-directed actions may thus become habitual responses due to overtraining (see Fig. 1). This shift from goal-directed to habitual avoidance has been linked to a shift from amygdala-dependent to amygdala-independent neural circuits (see Cain, 2019; LeDoux & Daw, 2018). As a consequence, habitual avoidance is assumed to be less sensitive to the reduction of the intensity of the US (i.e., devaluation of the US) or to changing outcome contingencies (i.e., contingency degradation; Robbins & Costa, 2017). Importantly, the transition from goal-directed to habitual responses and the insensitivity to outcomes may be one factor involved in the development of maladaptive avoidance in anxious individuals, which persists despite the absence of objective threat. Indeed, high levels of trait anxiety may be linked to a stronger shift towards habitual responding (see 3.1.1.1 Vulnerability traits).

2.1.4. Pavlovian-to-instrumental transfer (PIT)

So far, the discussed findings and theories were based on signaled avoidance, in which a defensive behavior is performed in response to the CS+ signaling an upcoming US. Instrumental defensive behavior can, however, also be acquired without a direct link to a warning signal. In a Sidman avoidance procedure, an aversive US is periodically presented unless a defensive action is performed, which then delays the US by a certain amount of time (see Sidman, 1953a; 1953b, 1962). Once acquired, such unsignaled avoidance responses can be influenced by a previously acquired CS+. This effect is known as Pavlovian-to-instrumental transfer (PIT; e.g., Corbit & Balleine, 2011; Holmes, Marchand, & Coutureau, 2010; Rescorla & Solomon, 1967). Mostly applied in appetitive learning, PIT paradigms involve two separate acquisition phases: Pavlovian acquisition of a stimulus-outcome association (CS–US) and instrumental acquisition of an unsignaled response-outcome association (defensive action – no US). In the subsequent transfer phase, Pavlovian CSs are presented during instrumental performance (for more details see Cartoni, Balleine, & Baldassarre, 2016; Holmes et al., 2010). Recent studies indicated that acquired defensive actions increase during presentation of fear-conditioned CSs when defensive actions were associated with the same aversive outcome (specific PIT) or a different aversive outcome as the Pavlovian CS (general PIT; Campese, McCue, Lázaro-Muñoz, LeDoux, & Cain, 2013; Cartoni et al., 2016; Nadler, Delgado, & Delamater, 2011). Several theories were proposed to explain these PIT effects, including, for example, the induction of a general motivational state facilitating motivation-congruent behavior and the indirect formations of stimulus-response associations (for a review see Cartoni et al., 2016). Irrespective of the exact mechanisms, these results highlight that the presence of a fear-conditioned CS may increase instrumental defensive behaviors despite the CS and behavior not being directly associated with each other. Thus, aversive PIT demonstrates an additional pathway how Pavlovian CSs may impact instrumental defensive behavior. As only few studies exist, little is known about potential moderators and its clinical relevance.

Summary. Taken together, different processes contribute to the impact of conditioned fear on the learning and expression of instrumental defensive behaviors (see Fig. 1). We highlighted relief learning as a process presumably reinforcing goal-directed defensive actions. The degree of these actions is determined by Pavlovian generalization of fear and Pavlovian-to-instrumental transfer. With repetition, a shift towards defensive habits may occur.

2.2. From instrumental defensive behaviors to fear responses

As shown in Fig. 1, we adopt a bi-directional relationship between conditioned fear and instrumental defensive behaviors, i.e., these instrumental defensive behaviors are not only influenced by but also systematically influence conditioned fear and fear responding. Next, we highlight that instrumental defensive behaviors can lead to an initial reduction of fear, but may also preserve or even elevate later fear responding.

2.2.1. Initial reduction of fear responses

There is substantial evidence supporting the notion that the availability of escape or avoidance responses can decrease fear responding. In humans, distinct defensive reactions, such as the startle response, decline prior to performance of goal-directed avoidance, which has been interpreted as a switch from attentive freezing to response preparation (e.g. Löw, Weymar, & Hamm, 2015; Wendt, Löw, Weymar, Lotze, & Hamm, 2017). Similarly, defensive freezing in rodents is negatively correlated with goal-directed avoidance (i.e., shuttle). Cain (2019) highlighted that defensive reactions may predominate during early training. However, when exposed to the instrumental contingencies, defensive reactions need to be inhibited in favor of acquiring and performing more goal-directed defensive responses (see also Löw et al., 2015; Wendt et al., 2017). After successful acquisition and sufficient training, the CS+ may then no longer represent a signal for unescapable threat but instead a signal for the opportunity to avoid threat (Cain, 2019). In this regard, rather hardwired defensive reactions need to be attenuated as they are incompatible with goal-directed actions.

Moreover, multiple studies demonstrated that threat expectancies, SCRs, and self-reported fear decrease as soon as human participants acquire an effective avoidance response (e.g., Van Uijen, Leer, & Engelhard, 2018; Vervliet & Indekeu, 2015; Pittig, 2019). Especially in humans, a reduction in fear responding due to the availability of effective instrumental defensive behaviors can be explained in terms of decreased threat expectancies. It has been repeatedly suggested that individuals acquire knowledge about the action-outcome contingencies during instrumental learning (Krypotos et al., 2015; Lovibond, 2006). In support, performing instrumental defensive responses decreases threat expectancies (De Houwer, Crombez, & Baeyens, 2005; Van Uijen et al., 2018). As proposed by Lovibond (2006) and Mitchell, De Houwer, and Lovibond (2009), a reduction in threat expectancy may in turn result in lower fear responding, which is supported by findings that instructed reduction of threat expectancies results in reduced SCRs (Hugdahl & Ohman, 1977; Lipp & Edwards, 2002). Hence, the reduction in threat expectancy due to the availability of effective instrumental defensive behaviors is a plausible mechanism that mediates fear reduction in humans.

Taken together, one potential mechanism by which avoidance may reduce fear responses is that certain defensive reactions are inhibited in favor of incompatible goal-directed actions. In humans, fear responses such as SCRs may also decrease due to a reduction of threat expectancies. After a history of overtrained defensive actions, responses may turn habitual. Habitual responding does not require the CS+ to elicit a fear response as it is automatically triggered via the S-R association. As no fear response is required for habitual avoidance, habitual avoidance speculatively does not reduce fear, but rather prohibits fear responses or keeps them to a low level.

2.2.2. Fear preservation

In clinical settings, excessive avoidance of feared stimuli and safety behaviors are considered major factors contributing to the maintenance of various anxiety disorders (e.g. Helbig-Lang & Petermann, 2010; Pittig, Treanor et al., 2018). They are believed to contribute to a vicious circle of initial fear reduction but a long-term preservation of fear. Indeed, experimental research suggests that goal-directed avoidance can lead to the preservation of fear responses (Lovibond et al., 2009; Pittig, 2019; Volders, Meulders, Peuter, Vervliet, & Vlaeyen, 2012). For example, participants that consistently showed goal-directed avoidance in the absence of an US (i.e., during extinction training) later showed elevated fear responses when avoidance became unavailable (Lovibond et al., 2009; Pittig, 2019).

Preservation of conditioned fear after extinction training can be explained by a mechanism called protection from extinction. In Pavlovian learning, protection from extinction refers to the phenomenon of extinction learning to a target stimulus being interfered by a Pavlovian conditioned inhibitor. For instance, when an excitatory stimulus (A+) and an established inhibitory stimulus (B-) are presented together during extinction (AB-), no extinction learning to the excitatory stimulus A takes place. This is evident by non-extinguished, preserved fear responding to stimulus A presented alone in a subsequent test (e.g., Lovibond, Davis, & O'Flaherty, 2000; McConnell & Miller, 2010; Soltysik, Wolfe, Nicholas, Wilson, & Garcia-Sanchez, 1983). As B already signals the absence of the US, no prediction error to the AB compound takes place during extinction and thus novel extinction learning to A is blocked (Rescorla, 2003). Therefore, it is said that stimulus A has been 'protected' from extinction learning.

Interestingly, protection from extinction can also arise from instrumental defensive behaviors. In a seminal study, participants were able to perform US-avoidance to one CS+ (A+) but not to another CS+ (C+) during extinction (Lovibond et al., 2009). In the subsequent test, when goal-directed avoidance was made unavailable for all stimuli, participants showed higher threat expectancies and SCRs to the stimulus for which avoidance was available (A). This increased fear responding during test can be interpreted as participants associating US omission during extinction to goal-directed avoidance, therefore preventing extinction learning to A. Protection from extinction is thus a mechanism of how instrumental defensive behaviors preserve conditioned fear in the absence of aversive outcomes.

Regarding habitual avoidance, it can be assumed that it also preserves fear by means of protection from extinction. Since habitual avoidance is triggered by the preceding CS+ (via S-R association), it should be automatically elicited by the CS+ and thereby prevent experiencing the non-occurrence of the US when avoidance is not performed. Moreover, as habits are less sensitive to their outcomes, defensive habits may persist even after some experience that the US does not occur when avoidance is not performed, resulting in ongoing habitual avoidance. However, to our knowledge, studies have not investigated the interaction between habitual avoidance and protection from extinction and are thus needed.

2.2.3. Increase of fear responding

Instrumental defensive responses not only preserve but may sometimes elevate fear responding (see Fig. 1). For instance, studies showed that the availability of goal-directed avoidance after Pavlovian extinction can trigger a partial return of threat expectancies (Van Uijen et al., 2018; Vervliet & Indekeu, 2015). Engelhard et al. (2015) demonstrated that goal-directed avoidance can elevate threat expectancies even to a safety stimulus: After Pavlovian fear acquisition, participants learned to perform an avoidance response to the CS+. Next, the avoidance response was made available for a CS-, which was never paired with a US. Participants who performed goal-directed avoidance to the CS- indicated higher threat expectancies to it in a subsequent test. This implies that instrumental defensive behaviors can indeed not only preserve but also elevate fear responding.

Different explanations may account for this finding. One plausible explanation is the use of "behavior as information". This explanation reflects that individuals may use their performance of defensive behaviors as a source of information on potential threat (see Gangemi, Mancini, & van den Hout, 2012; Van den Hout et al., 2014). Accordingly, performing avoidance or escape responses in face of a specific stimulus may be seen as an indicator of that stimulus being associated with danger. Gangemi et al. (2012) provide indirect support for this assumption in clinical samples: The authors asked patients suffering from different anxiety disorders and healthy controls to rate the perceived level of danger in several hypothetical situations. Results showed that patients, unlike healthy controls, tended to use information on safety-seeking behavior to infer the presence of danger. This difference was especially pronounced for scripts describing objectively safe situations. A subsequent replication study by Van den Hout et al. (2014) supported these findings. Accordingly, the use of behavior as information on potential threat may mediate the effect of instrumental defensive behaviors on fear responding, especially in clinical samples. Unlike protection from extinction, this mechanism has the potential to explain why performing instrumental defensive behaviors can elevate fear responding in face of objectively safe stimuli. Furthermore, an elevated use of instrumental defensive behavior as information in anxious individuals may initiate a vicious circle (cf. Gangemi et al., 2012): Performed avoidance and escape responses may induce enhanced perception of threat which in turn encourages further avoidance and escape responses until these responses turn habitual. However, empirical evidence is scarce and has only been shown for hypothetical situations. Using controlled human aversive conditioning paradigms may help to pinpoint the effect of "behavior as information" on subsequent fear responding.

The acquisition of fear towards objectively safe stimuli following instrumental defensive behaviors may also be explained in terms of cognitive dissonance (see Van Uijen et al., 2018). According to the cognitive dissonance theory (Festinger, 1957), two cognitive elements (e.g. knowledge about ourselves and our behavior) are dissonant if they contradict each other. In that sense, performing instrumental defensive behaviors in response to an objectively safe stimulus may result in cognitive dissonance (an unpleasant state which is, for example, not required for the behavior-as-information process). Individuals may then reduce this unpleasant state by aligning their threat beliefs to their performed behavior, resulting in elevated fear responses during subsequent encounters. In this regard, the cognitive dissonance explanation requires an unpleasant state after the performance of an instrumental defensive behavior to a known safe stimulus. In contrast, "behavior as information" would also reinforce an existing belief about threat, i.e., there is no need for an unpleasant state caused by a discrepancy between threat expectancy and behavior. Thus, although both explanations predict an increase of fear following instrumental defensive behaviors, they assume different underlying mechanisms.

Finally, not only the performance, but also the mere availability of goal-directed defensive behaviors may cause increased threat expectancies (Pittig, 2019; Van Uijen et al., 2018). The acquisition and expression of goal-directed avoidance are mediated by low threat expectancies when avoiding and high threat expectancies when not avoiding. After acquiring these expectancies to a CS+, the apparent availability of an avoidance response may function as a contextual cue signaling the presence of potential threat that needs to be prevented by performing an avoidance response to whatever stimulus an avoidance response is available (Vervliet & Indekeu, 2015). This may then in turn motivate the actual execution of instrumental defensive behaviors in response to the respective stimulus.

Taken together, the acquisition of fear responding as a consequence of instrumental defensive behavior can be explained in several ways. First, the performance of instrumental defensive behavior may be used as a source of information on potential threat. Second, performing instrumental defensive responses towards safe stimuli might induce cognitive dissonance. Third, the mere availability of instrumental defensive responses may signal potential threat. These different processes may not be independent from each other. Future research is necessary to examine these different explanations and their distinct contribution to the impact of instrumental defensive behaviors on conditioned fear. In addition, no studies investigate whether similar effects exist in habitual avoidance. In terms of clinical implications, this may inform how avoiding or escaping a fear-related stimulus after treatment may enhance the risk for relapse and how performing instrumental defensive behaviors towards novel stimuli or situations may contribute to the spread of fear.

3. Moderators for the relationship between fear and avoidance

The mechanisms underlying the bi-directional link between fear and instrumental defensive behaviors can be amplified or dampened by several moderating factors (see Fig. 1). These moderating factors can either be dispositional individual traits, transient intra-individual states, or external factors. All these factors may take effect via different pathways. First, some factors may increase or decrease conditioned fear and in turn indirectly increasing or decreasing the degree of subsequent instrumental defensive behaviors. Second, factors may directly increase or decrease instrumental defensive behaviors, which may in turn also modulate fear responding. Finally, factors may moderate the link between conditioned fear and instrumental defensive behaviors. We will highlight evidence for these pathways, although there is generally little research disentangling them. We will first review moderating factors that amplify the bi-directional link, followed by factors dampening the link.

3.1. Amplifying factors

3.1.1. Traits & inter-individual differences

3.1.1.1. Vulnerability traits. Trait anxiety. Trait anxiety refers to a stable predisposition to show negative emotional responses, such as fear, anxiety and worries, across situations, and has been widely agreed as a vulnerability factor for the development of anxiety disorders (Chambers, Power, & Durham, 2004; Gershuny & Sher, 1998; Jorm et al., 2000). Although numerous studies examining trait anxiety have focused on cognitive biases to threat (e.g., Butler & Mathews, 1987; MacLeod & Cohen, 1993; MacLeod & Mathews, 1988) and elevated threat appraisal in Pavlovian fear conditioning procedures (e.g., Chan & Lovibond, 1996; Gazendam, Kamphuis, & Kindt, 2013; Zinbarg & Revelle, 1989), there is surprisingly little work on the effect of trait anxiety on instrumental defensive behaviors. Some preliminary studies found that high trait anxious children showed more goal-directed avoidance to the CS + than their low anxious counterparts (Lau et al., 2012; Lau & Viding, 2007). Similarly, Pittig, Schulz et al. (2014) found that trait anxious individuals were more likely to avoid a behavioral option leading to CS+ presentations (i.e., CS-avoidance). More importantly, trait anxiety moderated the relation between fear acquisition and the degree of CS-avoidance in this study. High and low anxious individuals did not differ in differential SCRs towards the CSs, but interestingly, higher differential SCRs were associated with stronger CS-avoidance only in trait anxious individuals. This finding sits well with the literature where trait anxious individuals did not show increased fear responding to stimuli that clearly predicted an aversive US (e.g., Fahrenberg, Walschburger, Foerster, Myrtek, & Müller, 1983; Gazendam et al., 2013; Neary & Zuckerman, 1976; Wong & Lovibond, 2018). It therefore suggests that the impact of acquired fear on goal-directed avoidance is amplified in high trait anxious individuals.

In addition, some studies found that trait anxiety is associated with more goal-directed avoidance to a CS- (Gorka, LaBar, & Hariri, 2016; Vervliet & Indekeu, 2015), presumably due to impaired safety learning (Gazendam et al., 2013; Grillon & Ameli, 2001; Haaker et al., 2015; but see Haddad, Pritchett, Lissek, & Lau, 2012; Kindt & Soeter, 2014; Wong & Lovibond, in revision) or excessive fear generalization (Haddad et al., 2012). Moreover, a recent study found that trait anxious individuals were less flexible to update their outcome expectancies when the CS-US contingencies were switched (Browning, Behrens, Jocham, O'Reilly, & Bishop, 2015). This may potentially explain why trait anxiety is linked to deficits in extinction learning (e.g., Gazendam et al., 2013; Haaker et al., 2015), and speculatively leads to a higher degree of goal-directed avoidance.

Preliminary evidence also suggests that trait anxiety may elevate the acquisition of habitual avoidance (Flores, López, Vervliet, & Cobos, 2018). Amplified habitual avoidance behavior has also been found in persons with OCD (Gillan et al., 2014). Of note, however, the association between trait anxiety and habitual avoidance may be mediated by prospective intolerance of uncertainty (Flores et al., 2018) and null-findings have also been reported (Gillan et al., 2019). Clinical anxiety has also been associated with stronger habitual behavior (Alvares, Balleine, & Guastella, 2014; Alvares, Balleine, Whittle, & Guastella, 2016). However, these studies used an appetitive instead of an aversive habit paradigm. It thus seems that trait anxiety may not exclusively enhance defensive, but also appetitive habits. It has been proposed that trait anxiety is associated with the inefficient use of attentional resources, including deficits in inhibiting reflexive processes to threat as well as enhanced bottom-up processing of salient stimuli (Berggren & Derakshan, 2013; Berggren, Koster, & Derakshan, 2012; Derakshan & Eysenck, 2009; M. W.; Eysenck, Derakshan, Santos, & Calvo, 2007). This possibly facilitates a stronger shift towards habitual behavior in general. However, studies examining defensive and appetitive habits at the same time are missing.

In sum, findings suggest that trait anxious individuals do not show elevated fear acquisition, but stronger goal-directed avoidance in response to conditioned fear stimuli. Trait anxious individuals also show enhanced goal-directed avoidance to conditioned safety stimuli. Finally, trait anxiety may be associated with enhanced acquisition of habits, but future research is needed to examine whether this may be a general effect or whether trait anxiety might specifically enhance the acquisition of habitual avoidance behaviors.

Intolerance of uncertainty. Intolerance of uncertainty is suggested to be another vulnerability trait for the development of anxiety disorders (Boelen & Reijntjes, 2008; Dugas, Gagnon, Ladouceur, & Freeston, 1998; Fetzner, Horswill, Boelen, & Carleton, 2013). Individuals high in intolerance of uncertainty are characterized by having a bias towards evaluating uncertain or ambiguous situations negatively (Chen and Lovibond, 2016; Dugas, Schwartz, & Francis, 2004).

Only a few studies examined the effect of intolerance of uncertainty on goal-directed avoidance. Hunt et al. (2019) showed that higher intolerance of uncertainty was linked to higher threat expectancies to GSs that were similar to the CS+ and CS- to the same extent, therefore having the most ambiguous threat value. Importantly, intolerance of uncertainty positively moderated the relation between threat expectancies and avoidance to these GSs. Similarly, a recent study also found a positive association between intolerance of uncertainty and behavioral avoidance (San Martín, Jacobs, & Vervliet, 2019). Moreover, prospective intolerance of uncertainty, a facet of intolerance of uncertainty that is defined as actively seeking for certainty, was associated with more goal-directed avoidance to the CS + that unreliably predicted an aversive US, and surprisingly more goal-directed avoidance to the CS- during the instrumental learning phase (Flores et al., 2018). Importantly, the higher degree of US-avoidance among individuals high in prospective intolerance of uncertainty was observed even after the aversiveness of the US was devaluated. This suggests that prospective intolerance of uncertainty may also be associated with enhanced acquisition of habitual avoidance.

In sum, preliminary evidence suggests that intolerance of uncertainty amplifies goal-directed avoidance, via two possible routes. First, individuals high in intolerance of uncertainty show more fear responding to stimuli that have ambiguous threat value, therefore motivating a higher degree of goal-directed avoidance. Second, under threat ambiguity, intolerance of uncertainty moderates the link between acquired fear and goal-directed avoidance. Preliminary evidence also suggests that prospective intolerance of uncertainty enhances the acquisition of both goal-directed avoidance and habitual avoidance.

Anxiety sensitivity. Anxiety sensitivity refers to a predisposition to attribute physiological or physical sensations to anxiety symptoms (Reiss, 1987; Reiss, Peterson, Gursky, & McNally, 1986). It has been widely suggested as a vulnerability factor for the development of anxiety disorders (Olatunji & Wolitzky-Taylor, 2009; Plehn & Peterson, 2002). Preliminary evidence has linked anxiety sensitivity to risk-aversive decisions (Broman-Fulks, Urbaniak, Bondy, & Toomey, 2014) and self-reported avoidance of anxiety-provoking situations (e.g., traveling alone, speaking to an audience; Wilson & Hayward, 2006). However, little direct evidence is available on the role of anxiety sensitivity for instrumental defensive behaviors. Lebowitz, Shic, Campbell, Basile, and Silverman (2015) found that individuals high in anxiety sensitivity were more likely to avoid fear-related stimuli although this behavioral decision conflicted with the goal of the task. This elevated avoidance was found in the absence of differences in fear responses. The increase of goal-directed avoidance in the absence of differences in fear responding was conceptually replicated (Hunt et al., 2019). This pattern was interpreted as anxiety sensitive individuals being fearful of the physiological symptoms experienced during presentation of the fear-related stimuli (e.g., GSs that resemble CS+), which in turn increased the motivation to avoid. So far, no studies have examined the effect of anxiety sensitivity on habitual avoidance.

Neuroticism. Neuroticism refers to emotional instability, as individuals high in neuroticism tend to experience high levels of negative feelings like fear, anxiety, worry and frustration (Eysenck, 1947, 1967). It is moderately correlated with trait anxiety (Gray, 1981, 1982; Watson and Clark, 1984) and has been suggested to be closely associated with anxiety disorders (e.g., Watson, Gamez, & Simms, 2005). A seminal study showed that neuroticism is strongly linked to avoidance-focused goals (Elliot & Thrash, 2002). Moreover, Lommen, Engelhard, and van den Hout (2010) found that individuals high in neuroticism were more likely to avoid GSs that resembled the CS-. However, they did not specifically examine whether these individuals showed more Pavlovian fear generalization than individuals low in neuroticism. Thus, the effect of neuroticism on goal-directed avoidance remains largely unclear. It may be problematic that the construct of neuroticism includes different sub-constructs (such as anger or sadness, Costa & McCrae, 2008). It may thus be a too broad construct for a specific link to defensive behaviors. To our knowledge, no studies have examined the effect of neuroticism on habitual avoidance.

Summary vulnerability traits. Trait anxiety and anxiety sensitivity were found to moderate the link between fear responses and goal-directed avoidance, but not by directly amplifying acquired fear. Trait anxiety was also linked to increased fear to safety stimuli and therefore increased avoidance to them. In contrast, preliminary evidence has suggested that intolerance of uncertainty increases goal-directed avoidance to stimuli that have ambiguous threat value via two possible pathways: First, by directly increasing fear responding to these stimuli, therefore increasing the motivation for goal-directed avoidance, and second, by directly enhancing goal-directed avoidance to threat ambiguity. Moreover, preliminary evidence suggests that both intolerance of uncertainty and trait anxiety facilitate the acquisition of habitual avoidance.

To our knowledge, there are, however, no studies examining the role of vulnerability traits in the link from instrumental defensive behaviors to conditioned fear. It would be important for future research to address this gap, for instance, by investigating whether vulnerable individuals may be more likely to show fear preservation or increase in fear due to instrumental defensive behaviors. It is also worth mentioning that the effect of some vulnerability traits on the bi-directional relationship between fear and defensive behaviors, such as behavioral inhibition (Carver & White, 1994; Díaz & Pickering, 1993; Gomez, Cooper, & Gomez, 2000; Gray, 1970, 1994; Gray & McNaughton, 2003) has received less attention in aversive conditioning research (e.g., Avila & Parcet, 2000; Avila, Parcet, Ortet, & Ibáñez-Ribes, 1999). In addition, it needs to be clarified whether the different vulnerability factors are distinct moderators. Trait anxiety positively correlates with anxiety sensitivity (r = 0.46–0.53; McNally, 1999; McWilliams & Cox, 2001) and neuroticism (r = 0.7; D. Watson & Clark, 1984, while intolerance of uncertainty is positively correlated with anxiety sensitivity (r = 0.43–0.68; Carleton, Sharpe, & Asmundson, 2007; Laposa, Collimore, Hawley, & Rector, 2015). The different measures may thus assess a shared latent factor (i.e., anxiety proneness) that is moderating the relationship between conditioned fear and instrumental defensive behaviors. Although there is preliminary evidence for distinct pathways of different traits, future research needs to target the specificity of these traits. Furthermore, there is evidence showing that biased fear learning predicts subsequent anxiety symptoms (e.g., Lenaert et al., 2014; Waters, 2017). One may thus speculate that certain vulnerability factors could also be a consequence of atypical defensive behaviors (e.g., an individual persistently showing elevated defensive behaviors in early life may later be characterized as high trait anxious). Therefore, this potential reciprocal relationship between the aforementioned vulnerability factors and fear learning requires further investigation.

3.1.1.2. Sex and gender. Epidemiological studies consistently report that females are more likely to develop anxiety disorders than males (e.g., Bruce et al., 2005; Kessler et al., 1994; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). Preliminary evidence found greater activation in the amygdala when a feared stimulus was presented in females (McClure et al., 2004). While such findings may suggest a general effect of biological sex on fear learning, recent research points to a more complex relationship involving hormonal levels and contraceptives (e.g., Merz et al., 2018). For instance, estrogen has been found to enhance conditioned fear (e.g., Jasnow, Schulkin, & Pfaff, 2006; Matsumoto, Kasai, & Tomihara, 2018) and fear generalization (Lynch, Cullen, Jasnow, & Riccio, 2013). However, other findings did not find any effect of female hormones on fear acquisition (e.g., Graham & Milad, 2013; Milad et al., 2010). Regarding instrumental defensive behaviors, goal-directed avoidance seems to be enhanced in females (e.g., Sheynin et al., 2014; Speltz & Bernstein, 1976), even when avoidance conflicts with the goal of the task (Aupperle, Sullivan, Melrose, Paulus, & Stein, 2011). However, the contribution of menstrual cycles, hormones, and contraceptives need more detailed investigation to parallel research in Pavlovian fear learning (see Merz et al., 2018; Pittig, Treanor et al., 2018).

Besides biological sex, social gender role also plays an important role in fear learning and goal-directed avoidance. The construct “instrumentality” refers to one's tendency to strive for independence and accomplishment, which has been associated with the traditional masculine gender role. In contrast, “expressivity” refers to openness of emotion expression, which has been associated with the traditional feminine gender role (Block, 1983; Spence & Helmreich, 1978). Empirical studies showed that instrumentality is negatively associated with threat appraisal (Arrindell, Kolk, Pickersgill, & Hageman, 1993) while expressivity is positively associated with threat appraisal (Tucker & Bond, 1997; Zalta & Chambless, 2012). McLean and Hope (2010) found that higher levels of instrumentality were associated with a decrease in goal-directed avoidance in a BAT paradigm (but see Stoyanova & Hope, 2012). Furthermore, among biologically male individuals, those with higher levels of expressivity showed more goal-directed avoidance. Traditional gender-specific expectations that emphasize dependency and passivity for women and problem-focusing and instrumentality for men might result in differences concerning the reinforcement of corresponding behaviors during upbringing, rendering women especially prone to avoidant reactions in adolescence and adulthood (Bekker & van Mens-Verhulst, 2007; McLean & Anderson, 2009). However, there is, to the best of our knowledge, no controlled human aversive conditioning study examining the impact of gender roles on goal-directed or habitual avoidance.

In sum, one can speculate that the increase in goal-directed avoidance associated with female biological sex may result from enhanced fear acquisition, but investigations of direct effects are missing. Furthermore, female social gender role is also associated with a higher degree of goal-directed avoidance, but direct effects are unknown as well. Again, controlled investigations are missing, highlighting the usefulness of human aversive conditioning research to shed light on the impact of biological sex and gender roles on instrumental defensive behavior.

3.1.1.3. Age. Some anxiety disorders are more prevalent in adolescents than in adults (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012) and the age of onset for many anxiety disorders lies in childhood or early adolescence (Costello, Egger, & Angold, 2005). These findings suggest that age plays an important role in the development of anxiety disorders. In fact, rodent models have found that adolescents show enhanced conditioned fear to the CS+ during fear acquisition training (e.g., Hefner & Holmes, 2007; but see Ganella & Kim, 2014) and enhanced resistance in fear extinction (e.g. Hefner & Holmes, 2007; Kim, Li, & Richardson, 2011; McCallum, Kim, & Richardson, 2010; Pattwell et al., 2012; Zbukvic, Park, Ganella, Lawrence, & Kim, 2017). Adolescent rodents also showed more goal-directed avoidance (e.g. Lynn & Brown, 2010; Stone & Quartermain, 1997).

Correspondingly, human studies also suggest that adolescents compared to children show elevated fear acquisition and more fear generalization (Glenn et al., 2012), although the findings are not consistent (see Waters, Theresiana, Neumann, & Craske, 2017; for a review see; Pittig, Treanor et al., 2018). Regarding instrumental defensive behaviors, preliminary evidence suggests that socially anxious adolescents more frequently avoid certain social situations compared to children (Rao et al., 2007; Sumter, Bokhorst, & Westenberg, 2009). Adolescents and children also seem to rely more heavily on habitual as opposed to goal-directed learning than adults (Decker, Otto, Daw, & Hartley, 2016). Combined, it may be speculated that these findings relate to increased goal-directed avoidance and a faster development of habitual avoidance in adolescents, but research is missing. Furthermore, there is a lack of research on how age may affect the impact of instrumental defensive behavior on fear learning, for instance, whether adolescents show a stronger increase of fear following instrumental learning.

3.1.1.4. Adverse life events and high threat environments. Life adversities, such as physical or psychological abuse and emotional neglect, have been linked to a higher risk of developing anxiety disorders (e.g., Spinhoven et al., 2010). Maltreated children showed poorer SCR discrimination between CS+ and CS- compared to non-maltreated children, especially during early fear acquisition training (McLaughlin et al., 2016). This may be explained by enhanced generalization of fear from CS + to CS-. Likewise, individuals who were recently exposed to trauma compared to non-exposed individuals, showed indiscriminative threat expectancies to both CS+ and CS- during fear acquisition training (Harnett et al., 2018). In contrast, no differences were found in SCRs and threat expectancies to the CSs between healthy trauma exposed and healthy non-exposed individuals (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007). However, healthy trauma-exposed individuals preferred an option associated with a CS- over another option associated with a CS+ during a subsequent forced-choice test, whereas non-exposed individuals showed no preference. This may tentatively hint at elevated goal-directed avoidance in trauma-exposed individuals. Early life stress has also been found to predict higher probability of performing habitual avoidance behaviors in one study (Patterson, Craske, & Knowlton, 2019).

The likelihood of experiencing adverse life events or harm is higher in high-threat environments. Preliminary studies showed that individuals living in high threat environments showed more self-reported avoidance intentions (e.g., Johnson, 2019; Shapira, Aharonson-Daniel, & Bar-Dayan, 2018). It can be hypothesized that individuals in high-threat environments may thus be more prone to respond with goal-directed avoidance or to develop habitual avoidance, which may be considered as adaptive in their living environment. However, this link has not yet been examined. In sum, more detailed examination of direct and indirect effects of adverse life events and high-threat environments on instrumental defensive behaviors are needed.

3.1.2. Intra-individual states

3.1.2.1. State anxiety. State anxiety refers to an unpleasant, transient emotional state of one's subjective apprehension and the activation of physiological activity to adverse or threatening situations (Spielberger, 1966, 1972). It has been widely accepted that the amount of state anxiety experienced is modulated by the individual level of trait anxiety (Spielberger, 1975). However, some studies suggested that the induction of state anxiety per se can affect fear learning (e.g., Dibbets & Evers, 2017; Vriends et al., 2011). After state anxiety induction, participants showed non-discriminative threat expectancies to both CS + and CS- during fear acquisition training and fear extinction (Dibbets & Evers, 2017), as well as a general elevation in skin conductance responding to both CSs during fear extinction (Vriends et al., 2011). These patterns were presumably due to a deficit in inhibiting fear responses or an enhancement of fear generalization from CS + to CS- caused by a heightened state of anxiety. Supporting the former interpretation, participants high in state anxiety failed to transfer the safety value of an inhibitory stimulus in a conditional discrimination paradigm (Liao & Craske, 2013). Furthermore, state anxiety was also associated with stronger return of fear via reinstatement, evident in both cue-conditioning (Kuhn, Mertens, & Lonsdorf, 2016) and contextual conditioning paradigms (Glotzbach-Schoon, Andreatta, Mühlberger, & Pauli, 2015). This effect was presumably due to fear memory in the reinstatement test being more likely to be retrieved and expressed than the extinction memory, since both fear memory and state anxiety are characterized by negative valence (i.e., mood congruent effect, Lewis and Critchley, 2003).

Regarding instrumental defensive behaviors, preliminary evidence showed that participants with high state anxiety were more likely to use avoidance-oriented coping strategies when confronting hypothetical stressful situations (Rutherford & Endler, 1999), suggesting that state anxiety increases behavioral avoidance. However, to our knowledge, there are no studies on the effect of state anxiety induction on instrumental defensive behaviors within a human aversive conditioning framework.

Regarding habitual avoidance, state anxiety may shift the balance from goal-directed avoidance towards habitual avoidance learning (see impact of stress below). There are, however, no studies available on the effect of state anxiety on the degree of habitual avoidance learning. Future research using controlled human aversive conditioning paradigms may shed light on these speculations.

3.1.2.2. Stress. A considerable amount of research on the effect of stress on Pavlovian fear learning is available (see Aubry, Serrano, & Burghardt, 2016; Bowers & Ressler, 2015). Rodent studies have shown that chronic stress or acute stress exposure prior to or after fear acquisition training enhances conditioned fear to the CS+ (see Aubry et al., 2016; Raio & Phelps, 2015; Rodrigues, LeDoux, & Sapolsky, 2009 for a review). Furthermore, administration of stress hormones, such as norepinephrine, increases conditioned fear in a test following fear acquisition training (Gazarini, Stern, Carobrez, & Bertoglio, 2013; LaLumiere, Buen, & McGaugh, 2003; Roozendaal et al., 2006; but see; Bush, Caparosa, Gekker, & LeDoux, 2010; Lee, Berger, Stiedl, Spiess, & Kim, 2001). In rodents, stress also plays an important role in regulating instrumental defensive behaviors. Rodents showed increased passive avoidance when stress hormones were administered after fear acquisition training (Ferry & McGaugh, 1999; Izquierdo, Barros, Medina, & Izquierdo, 2002; Liang, Juler, & McGaugh, 1986; McIntyre, Hatfield, & McGaugh, 2002; Roozendaal & McGaugh, 1997). The observed enhanced passive avoidance is presumably due to enhanced acquired fear caused by the induction of stress (see Rodrigues et al., 2009).

In humans, stress was also found to facilitate the acquisition of fear (Goodman et al., 2018; Grillon, Cordova, Morgan, Charney, & Davis, 2004; Jackson, Payne, Nadel, & Jacobs, 2006). However, the role of stress on conditioned fear has been found to be more sex specific. While some studies found that stress exposure prior to fear acquisition training facilitates the acquisition of conditioned fear only in males (Zorawski, Blanding, Kuhn, & LaBar, 2006; Zorawski, Cook, Kuhn, & LaBar, 2005), other studies found such facilitation only in females taking oral contraceptives (Merz et al., 2010, 2013). Surprisingly, to our knowledge, there are almost no studies examining the role of stress on goal-directed avoidance in humans. Using a computerized approach-avoidance task, where participants were asked to collect as many points as possible while avoiding being caught by a virtual predator that would result in a loss of points, Vogel and Schwabe (2019) found that acute stress enhanced goal-directed avoidance. However, some neuroimaging studies found that stress reduces reward-related responses (e.g., Arnsten, 2009; Ossewaarde et al., 2011; Rygula et al., 2005), therefore the apparent increase in goal-directed avoidance could be potentially driven by a reduction of the motivation to gain rewards. Moreover, the specific source of stress and its link to defensive behaviors may be crucial for how stress modulates defensive behavior. For example, stress induced by food deprivation has been shown to reduce defensive behavior towards a predator to obtain food (Choi, Kim, & Jeansok, 2010). Therefore, more studies are needed to delineate the effect of stress on goal-directed avoidance in humans.

In humans, acute stress also resulted in a bias towards habitual compared to goal-directed behavior (Schwabe & Wolf, 2009, 2013; Wirz, Bogdanov, & Schwabe, 2018). Some studies found effects of acute stress only in individuals with certain characteristics such as low working memory (Otto, Raio, Chiang, Phelps, & Daw, 2013), high cortisol reactivity (Smeets, van Ruitenbeek, Hartogsveld, & Quaedflieg, 2019) or more frequent stressful life events (Radenbach et al., 2015). These findings suggest that the amplifying effect of stress on habitual behavior may be specific for vulnerable individuals. One large online study did not find an association between chronic stress and habitual behavior after controlling for compulsivity (Gillan et al., 2019). Direct investigations of stress as a potential moderator in the relationship between conditioned fear and habitual avoidance are missing so far.

Collectively, stress seems to enhance goal-directed avoidance in rodents. However, only few studies examined the role of stress in goal-directed avoidance in humans. The induction of stress has been found to favor habitual behavior over goal-directed behavior, however, results are not specific for avoidance and were found to have limited generalizability. Future studies could further investigate the role of stress in the bi-directional link between fear and instrumental defensive behaviors. For instance, it is still unclear whether stress can directly increase the degree of goal-directed avoidance, or whether it increases goal-directed avoidance only by enhancing fear learning. Furthermore, the mechanism underlying the putative shift from goal-directed avoidance to habitual avoidance caused by acute stress is still largely unknown.

3.1.3. External factors

In rodents and humans, a wealth of factors regarding the learning experience have been examined as external factors. For example, learning and expression of instrumental defensive behaviors are influenced by reinforcement schedules, CS-US contiguity and contingency, the amount of learning trials, intensity or valence of the US, preparedness of the CSs, and many more. We thus only highlight some factors and refer readers to a seminal overview (Bouton, 2016). In addition, threat imminence strongly determines which type of defensive behavior is shown (e.g., goal-directed actions are linked to lower threat imminence). As excellent recent reviews exist (e.g., Mobbs, 2018), we will not discuss threat imminence here.

3.1.3.1. Unsignaled US. A signaled US refers to an US (semi-)reliably predicted by a preceding CS+ (cue conditioning), while an unsignaled US refers to an US not predicted by a preceding CS + at all (e.g., during context conditioning). Typically, responding in a context with unsignaled USs is interpreted as anxiety-like responding (compared to fear responses to a distinct CS). Findings in rodent studies suggest that an unsignaled US is more aversive than a signaled US. For instance, rodents showed more anxiety-like responding in a context where unsignaled USs were administered compared to another context where a US was preceded by a CS (e.g., Fanselow, 1980; Marlin, 1981). Rodents also showed more passive avoidance to the unsignaled context than to the signaled context (e.g., Abbott, 1985; Badia, Harsh, & Abbott, 1979; Herry et al., 2007; Odling-Smee, 1975). Similar to findings in rodents, humans show increased anxiety-like responding to unsignaled USs compared to signaled USs. In a seminal study, human participants showed more anxiety-like responding in an experimental room where they previously received unsignaled USs than in a room where they received signaled USs (Grillon & Davis, 1997). Subsequent studies replicated increased anxiety-like responding to unsignaled contexts (e.g., Ameli, Ip, & Grillon, 2001; Andreatta et al., 2015; Grillon, Baas, Lissek, Smith, & Milstein, 2004; Vansteenwegen, Iberico, Vervliet, Marescau, & Hermans, 2008).

Surprisingly, there is little evidence regarding the role of unsignaled USs in goal-directed avoidance in humans. Grillon, Baas, Cornwell, and Johnson (2006) utilized a virtual reality (VR) conditioning paradigm, where participants were guided through three virtual rooms, including a signaled context, an unsignaled context, and a no-US context. Participants showed increased anxiety-like responding to the unsignaled context compared to the other two contexts. More importantly, participants more frequently avoided the unsignaled context than the other contexts. Glotzbach, Ewald, Andreatta, Pauli, and Mühlberger (2012) found similar results: participants avoided the unsignaled context more frequently than the signaled and the no-US contexts in a VR environment. Moreover, higher self-reported anxiety and arousal ratings to the unsignaled context predicted higher subsequent goal-directed avoidance. In sum, when an aversive US is not signaled by a preceding warning signal (e.g., CS+), anxiety-like responding and behavioral avoidance are enhanced. However, future studies are required to unravel the effect of unsignaled US on behavioral avoidance, specifically, whether an unsignaled US enhances behavioral avoidance directly or by increasing anxiety-like responding.

3.1.3.2. Effectiveness of instrumental defensive behavior. The effectiveness of avoidance and escape refers to how reliably the response prevents or cancels the aversive event. It mediates both the frequency of goal-directed avoidance and escape as well as the initial impact of goal-directed defensive behavior on fear. Xia, Dymond, Lloyd, and Vervliet (2017) recently manipulated the effectiveness of goal-directed avoidance between participants by making it 0%, 25%, 50%, 75%, or 100% effective in preventing an aversive US (see also Olson, Davenport, & Kamichoff, 1971). Overall, participants acquired high rates of avoidance, which were reduced only under near ineffectiveness (i.e., 0% and 25%). These differences in avoidance frequency remained stable under extinction. Initially, threat expectancies inversely correlated with effectiveness, i.e., lower effectiveness was associated with higher threat expectancy. Thus, the effectiveness of instrumental defensive behavior influences its initial impact on fear responding. Interestingly, threat expectancy declined during subsequent US absence for effectiveness of 50% or lower, whereas expectancies remained low under highly effective avoidance (75 and 100%). This may suggest that partial effectiveness of goal-directed avoidance may reduce protection from extinction, which was, however, not tested. Further research is needed to shed more light on the impact of this factor.

3.2. Dampening factors

Next, we will review traits and individual differences, intra-individual states, and external factors that dampen the link between fear learning and instrumental defensive behaviors. Overall, there is little research in this area, highlighting a current research gap.

3.2.1. Traits & individual differences

3.2.1.1. Dampening traits. *Distress tolerance.* Distress tolerance is a construct summarizing the capacity to experience and withstand negative psychological states (see Simons & Gaher, 2005). Individuals with low distress tolerance are assumed to perceive distress as unbearable and are highly motivated to avoid negative states (Simons & Gaher, 2005). Consequently, it is plausible to assume that high distress tolerance should dampen goal-directed avoidance. Hunt, Cooper, Hartnell, and Lissek (2017) recently investigated distress endurance, a related construct characterized by willingness to maintaining goal pursuit despite discomfort and distress, which is a facet of experiential avoidance (Gámez, Chmielewski, Kotov, Ruggero, & Watson, 2011). Specifically, the impact of distress endurance on costly goal-directed avoidance to the original CS + as well as to GSs was examined. Distress endurance was associated with less avoidance to GSs for some, but not all avoidance measures. Interestingly, behavioral avoidance as one facet of experiential avoidance was not associated with goal-directed avoidance. This finding might indicate that the reduction of costly avoidance is less related to general avoidance tendencies under distress, but to the capability of facing distress in favor of an alternative goal or outcome. Alternatively, self-reports of distress avoidance and human aversive conditioning models may not measure the same features of goal-directed avoidance. Thus, replications are required to pinpoint the distinct contributions.

Another recent study provided evidence that distress tolerance may modulate goal-directed avoidance via differences in relief responses (Vervliet et al., 2017). Specifically, individuals with low compared to high distress tolerance showed a tendency for more goal-directed avoidance to the CS-. More interestingly, individuals high in distress tolerance showed a decrease in relief after US omission across trials, while those low in distress tolerance showed a sustained level of relief responding. Therefore, distress tolerance may play an important role in modulating goal-directed avoidance by modulating relief learning.

Sensation seeking. Sensation seeking refers to a personality trait where an individual actively seeks for sensory stimulation, even when it involves a high level of risk taking (Zuckerman, 1994). High sensation seeking has been associated with risky activities, such as extreme sports (e.g., Campbell, Tyrrell, & Zingaro, 1993; Hymbaugh & Garrett, 1974; Straub, 1982), law breaking (Arnett, 1996) and unsafe sexual behavior (Wagner, 2001). Conventionally, research on sensation seeking has been focused on its association with substance abuse and pathological gambling (e.g., Hittner & Swickert, 2006; Milosevic & Ledgerwood, 2010). However, some research suggested that sensation seeking acts as a resilience factor against the development of PTSD after traumatic experiences (Neria, Solomon, Ginzburg, & Dekel, 2000; Solomon, Ginzburg, Neria, & Ohry, 1995). In fact, individuals high in sensation seeking reported lower threat estimation and self-reported fear to dangerous activities (Franken, Gibson, & Rowland, 1992). Individuals high in sensation seeking also showed a lower level of EMG startle responses and skin conductance responses to threatening images than individuals low in sensation seeking (Lissek & Powers, 2003).

Preliminary evidence also suggested that individuals high in sensation seeking showed decreased goal-directed avoidance (Norbury, Kurth-Nelson, Winston, Roiser, & Husain, 2015; Norbury, Valton, Rees, Roiser, & Husain, 2016). Participants first learned the amount of reward predicted by each stimulus. In the following test phase, half of these stimuli were associated with a 75% chance of receiving an aversive US

(CSs+) whilst the other half were not associated with aversive outcomes (CSs-). CSs+ and CSs- were always presented in pairs on each test trial, and participants were asked to choose one of the CSs on every test trial. Individuals high in sensation seeking were more likely to approach the CS + than those low in sensation seeking, even when approaching the CS + resulted in lower gain (e.g., when a low-reward CS+ was paired with a high-reward CS-). This suggests that individuals high in sensation seeking are less likely to show goal-directed avoidance in tasks including both aversive and appetitive outcomes. However, it remains unclear whether sensation seeking generally reduces avoidance or whether the effect is limited to goal-directed avoidance in mixed-outcome situations. To our knowledge, no research directly investigated the effect of sensation seeking on fear learning and goal-directed or habitual avoidance within human aversive conditioning. However, based on the aforementioned findings, we speculate that sensation seeking reduces the level of acquired fear and therefore reduces subsequent behavioral avoidance or increases goal-directed approach. Future studies may also investigate whether sensation seeking directly affects instrumental defensive behaviors.

Self-efficacy. Self-efficacy has been defined as the belief to be able to perform a behavior that effectively produces a desired outcome (Bandura & Locke, 2003). Higher self-efficacy has been found to enhance fear extinction learning (Zlomuzica, Preusser, Schneider, & Margraf, 2015). In another study, experimentally induced low perceived self-efficacy was associated with a decreased discrimination between CS+ and CS- during acquisition, but not during extinction (Raeder, Karbach, Struwe, Margraf, & Zlomuzica, 2019). These studies provide insights that higher self-efficacy may facilitate extinction and discriminative learning. However, replications and further understanding of the underlying processes are needed. Especially, it remains unclear whether the effect of self-efficacy on fear learning can be translated into instrumental defensive behaviors. Regarding direct effects, we speculate that high self-efficacy may elevate an individual's confidence in their ability to confront threat, and thereby reduces goal-directed avoidance. Indirect evidence comes from studies showing that self-efficacy is positively correlated with approaching feared stimuli in exposure treatments in acrophobia (Williams, Turner, & Peer, 1985). In a cross-sectional survey, lower self-efficacy was associated with an increased tendency to use dysfunctional coping strategies when confronted with anxiety-provoking situations (Thomasson & Psouni, 2010). These findings tentatively suggest that high self-efficacy may dampen instrumental defensive responses.

However, high self-efficacy beliefs concerning the performance of an avoidance response may theoretically elevate the degree of avoidance (i.e., strong beliefs that one is able to perform the required behavior to prevent a threat). Ng and Lovibond (2019) found that participants reported less anxiety when intending to perform a simple goal-directed avoidance response, for which they held high self-efficacy beliefs, compared to a more difficult response, for which they held lower self-efficacy beliefs. Self-efficacy beliefs moderated the relationship between avoidance intentions and fear reduction. Combined, the moderating effect of self-efficacy may depend on whether self-efficacy beliefs target avoidance or approach behaviors. Finally, a higher degree of avoidance may hinder individuals from experiencing that they can effectively deal with fear and threat. In turn, a higher degree of avoidance may also lower self-efficacy beliefs. However, to the best of our knowledge, this has not been tested so far. Taken together, future research is needed to pinpoint a potentially moderating effect of self-efficacy on the degree of instrumental defensive behaviors. Such research could extend the current models of instrumental learning. Besides the expected outcome and its value, beliefs about one's ability to perform the action may be an additional factor involved in the instrumental learning and expression of human defensive actions.

3.2.2. Intra-individual states

3.2.2.1. Positive affect. Positive affect refers to positive emotions such as determination, enthusiasm, interest and joy (Watson & Clark, 1984). Positive affect has long been suggested to enhance encoding (e.g., Clore & Huntsinger, 2007; Craik & Lockhart, 1972) and retrieval of new memories (Craik, 2002). Recently, it has been suggested that positive affect enhances inhibitory learning (Meulders, Meulders, & Vlaeyen, 2014; Zbozinek & Craske, 2017a). In fact, recent evidence has shown that positive affect reduced reinstatement and reacquisition of fear (Zbozinek & Craske, 2017b; Zbozinek, Holmes, & Craske, 2015). Induction of positive affect after fear acquisition training also reduced the generalization of pain-related fear (Geschwind, Meulders, Peters, Vlaeyen, & Meulders, 2015). Surprisingly, to our knowledge, no study has examined the effect of positive affect on the degree of instrumental defensive behaviors. Based on findings of reduced fear generalization and enhanced inhibitory learning, it is speculative, but possible, that the induction of positive affect indirectly dampens goal-directed avoidance. However, it remains untested whether positive affect may directly reduce goal-directed avoidance. In addition, little is known about the impact of positive affect on habitual avoidance.

3.2.3. External factors

3.2.3.1. Cost of avoidance and incentives for competing behavior. Past studies on fear-driven avoidance mostly incorporated low to no costs to perform avoidance or safety behavior (e.g., Dymond et al., 2014; Lovibond et al., 2009; Lovibond, Saunders, Weidemann, & Mitchell, 2008; Vervliet et al., 2017; Vervliet & Indekeu, 2015). These studies elegantly demonstrated how conditioned fear motivates goal-directed avoidance when it is thought to be the sole determinant of behavior. However, low-cost goal-directed avoidance barely resembles costly, maladaptive avoidance among patients with anxiety disorders, for whom avoidance is linked to severe impairments.

More recent studies thus incorporated costs for fear-driven goal-directed avoidance (e.g., Pittig, Brand, Pawlikowski, & Alpers, 2014; Pittig, Schulz et al., 2014; Van Meurs et al., 2014). Incorporating costs compared to no costs clearly reduces goal-directed avoidance (Pittig, 2019; Pittig & Dehler, 2019; Pittig & Scherbaum, 2019; Rattel, Miedl, Blechert, & Wilhelm, 2017). Similarly, avoidance of pain-related stimuli is reduced when goal-directed avoidance inflicts costs (e.g., Claes, Crombez, & Vlaeyen, 2015; Claes, Vlaeyen, & Crombez, 2016; Van Damme, van Ryckeghem, Wyffels, van Hulle, & Crombez, 2012). Indeed, multiple studies provided direct evidence for an inverse association between costs and the degree of goal-directed avoidance – the higher the cost of avoidance, the less likely participants avoided (e.g., Pittig, 2019; Pittig & Dehler, 2019; Pittig & Scherbaum, 2019; Rattel et al., 2017; Sierra-Mercado et al., 2015; Talmi, Dayan, Kiebel, Frith, & Dolan, 2009). While some of these studies used temporal delay as costs (e.g., Rattel et al., 2017), performing a non-avoidance or approach response was associated with real or hypothetical monetary rewards in others (e.g., Claes et al., 2016; Pittig, 2019; Pittig & Dehler, 2019). These latter studies thus showed that incentives for a competing behavioral response trigger fear-opposite actions in healthy participants. We recently demonstrated that this incentive-based reduction of goal-directed avoidance does not directly modulate conditioned fear, but initiates fear extinction as soon as the aversive outcome is absent. In this regard, costs of avoidance and incentives for competing goal-directed behavior can prevent protection from extinction (Pittig, 2019).

The moderating role of costs on goal-directed avoidance is rather unclear among individuals with anxiety disorders. Individuals with anxiety disorders often show excessive avoidance despite high costs of this behavior (e.g., North et al., 2004; O'Donnell, Elliott, Lau, & Creamer, 2007; White & Barlow, 2002). One explanation may be that costly, maladaptive avoidance among patients is generally driven by higher threat appraisal or overprediction of fear (Britton, Lissek, Grillon, Norcross, & Pine, 2011; Butler & Mathews, 1983; Cox & Swinson, 1994; Rachman, 1994). Alternatively, individuals with high or clinical anxiety may be less sensitive to rewards competing with threat. For example, spider fearful compared to non-fearful individuals more frequently avoided spider stimuli despite costs when reward contingencies were ambiguous (Pittig et al., 2014), but equally frequently approached these stimuli for unambiguous high monetary or social rewards (Pittig, Hengen, Bublatzky, & Alpers, 2018). These findings fit with preliminary findings about a bias towards punishment sensitivity in individuals with anxiety disorders. Sheynin et al. (2017) instructed participants to control a spaceship and fire at targets to gain hypothetical rewards. Participants were also instructed that, when an enemy ship appeared, they had 5 s to get to a safety shelter before losing their reward. Female individuals with severe PTSD symptoms were quicker to avoid during this warning period, reducing their rewards. This pattern suggests that females with severe PTSD symptoms might be more sensitive to punishment and less sensitive to reward than healthy females, which is consistent with some previous findings (for a review see Nawijn et al., 2015). The over-sensitivity to punishment may help to explain the clinical observation that patients with anxiety disorders often engage in maladaptive goal-directed avoidance despite of its costs.

In conclusion, costs of goal-directed avoidance crucially modulate the degree of goal-directed avoidance and prevent protection from extinction, at least in healthy individuals. However, individuals with high or clinical levels of anxiety often show excessive goal-directed avoidance irrespective of costs. This pattern may be due to generally elevated threat expectancies, a higher sensitivity to punishment and lower sensitivity for competing rewards, or a combination of all these factors. Finally, little is known about the impact of costs on habitual avoidance. As habits are rather insensitive to their outcomes, their degree should be less sensitive to costs. However, costs of avoidance or incentives for competing approach may slow down the shift from goal-directed actions to habits or increase goal-directed control of behavior. Interestingly, a possible tendency to acquiring stronger habitual avoidance in individuals with high or clinical anxiety may interact with a higher sensitivity to punishment vs. rewards, as both processes tap into the inflexibility and maladaptivity of excessive avoidance in clinical anxiety.

3.2.3.2. Social demand and social reinforcement. Two social factors, namely social demand and social reinforcement, have been suggested to impact goal-directed avoidance. Corresponding studies mostly used behavioral approach tests (BATs), which usually involve participants to physically approach a fear-related object or situation. Goal-directed avoidance is conventionally measured as distance or time of approach (Lang and Lazovik, 1963).

Social demand is regarded as an individual behaving in a way that is desired by another social figure. Empirical studies induced social demand in individuals with specific phobias by explicitly informing them that it was expected that they successfully approached or touched fear-related objects (e.g., snake, rat). Induction compared to no induction of social demand resulted in lower self-reported fear and avoidance (Bernstein & Nietzel, 1974; Miller & Bernstein, 1972; Smith, Diener, & Beaman, 1974; Speltz & Bernstein, 1976). However, it was impossible to distinguish whether social demand genuinely decreased fear and thereby avoidance, or whether participants felt pressured to approach and provided socially desirable self-report. The latter explanation suggests that social demand only reduces goal-directed avoidance as long as it is present. To our knowledge, there are no studies examining social demand in human aversive conditioning, which would allow a more systematic investigation of conditioned fear and goal-directed avoidance.

Social incentives and reinforcement are intrinsically rewarding (Bandura & Walters, 1963; Baumeister & Leary, 1995), and have been suggested to play an important role in successful treatment (e.g., Krasner, 1962). BAT studies showed that patients with specific phobias who received social reinforcement (e.g., verbal praise after every attempt to approach a fear-related object) were less likely to avoid (Barlow, Agras, Leitenberg, & Wincze, 1970; Leitenberg, Agras, Barlow, & Oliveau, 1969; Wagner & Cauthen, 1968; but see Suinn, Jorgensen, Stewart, & McQuirk, 1971). More recently, Pittig, Hengen, et al. (2018) and Pittig, Treanor, et al. (2018) found that symbolic social incentives reduced goal-directed avoidance to spider stimuli among spider fearful individuals, which was associated with a decrease in self-reported fear. The findings suggest that social incentives, similar to non-social incentives, can initialize behavioral approach, which may subsequently promote extinction learning. However, goal-directed avoidance returned once social incentives were discontinued and self-reported fear was still high, suggesting that more training may be necessary for long-term effects.

In conclusion, both social demand and social incentives have been shown to reduce avoidance in behavioral tests. However, the underlying mechanism remains unclear. Future studies could examine whether social demand and reinforcement decreases goal-directed avoidance by genuinely decreasing fear, or by exerting demand characteristics to an individual.

3.3. Summary of moderators

Empirical evidence on several factors that could either amplify or dampen instrumental defensive behaviors is available. For example, vulnerability traits such as trait anxiety or intolerance of uncertainty have been found to amplify instrumental defensive behaviors. It remains, however, unclear whether these factors are unique moderators or whether their impact can be better explained by a joint latent factor (such as anxiety proneness). In addition, biological sex and social gender roles also seem to modulate instrumental defensive behaviors; however, the underlying mechanisms are largely unknown. Other factors such as costs as well as incentives or social demands for competing behaviors dampen goal-directed avoidance. Generally, there is much less research on dampening factors, highlighting a current gap with important implications. Most importantly, our discussion oftentimes relied on Pavlovian fear learning research, speculating that differences in acquired fear may result in different instrumental defensive behaviors. Additionally, some evidence is based on more naturalistic tests such as BATs. Although they offer good external validity, controlled investigations of processes possibly underlying a moderating effect are oftentimes missing. Using human aversive conditioning as a controlled, laboratory-based model offers a unique opportunity to close these gaps about the interactive modulation of fear learning and instrumental defensive behaviors. In this framework, research could aim to pinpoint at which part of the stimulus-response-outcome (S-R-O) processes a specific moderator acts. Whereas some moderators may modulate the strength of the CS-US association (S–O), thereby increasing conditioned fear and in turn defensive actions, others may increase the value of the outcome (i.e., US omission), or learning of the action-outcome contingency. Finally, most previous research on moderators of human instrumental defensive behavior explicitly focuses on goal-directed avoidance. Research on habitual avoidance is generally scarce and should therefore be addressed by future research.

4. Research and clinical implications

There are two main areas of implications. First, understanding moderators for the bi-directional link between human fear learning and instrumental defensive behaviors provides insights into risk factors for the development of anxious psychopathology, prevention efforts, and treatment. Second, different experimental models and clinical interventions can be mapped onto distinct types of defensive behavior and their underlying learning processes (see Fig. 1). In this way, a more precise matching helps to develop more nuanced models and interventions to reduce pathological behaviors and ultimately offer insights for individualized treatments. It also helps to better translate experimental findings to clinical use as well as to develop new experimental models for existing clinical interventions to optimize a reciprocal process of psychotherapy research (see Richter, Pittig, Hollandt, & Lueken, 2017). An exhaustive discussion about these implications is beyond the scope of this review. We thus highlight major points.

4.1. Moderators as risk or resilience factors

Factors moderating the link between conditioned fear and instrumental defensive behaviors are important to better understand under which circumstances which individual expresses which degree of defensive behaviors. While strong defensive behaviors are adaptive in some cases (e.g., under ongoing threat), the development of intense, widespread defensive behaviors, which persist in the absence of threat, is pathological and a key feature of all anxiety and related disorders (e.g. Craske et al., 2009; Craske et al., 2017). Clinically, knowledge about moderating factors thus helps to explain why, following the same aversive experience, some individuals do develop pathological behaviors and others do not. In this regard, amplifying factors may be seen as risk factors and dampening factors as resilience factors. Likewise, moderating factors for the impact of defensive behaviors on fear learning inform our understanding of risk and resilience factors for the long-term perseverance and increase in fear. There is some evidence on how certain factors such as trait anxiety and intolerance of uncertainty, or a lack of incentives for competing behaviors, modulate the link between fear and defensive behaviors. These factors may help to identify individuals at risk for anxious psychopathology and inform prevention efforts. Specifically, individuals showing risk factors to develop pathological defensive behaviors could be educated about the negative long-term effects of pathological defensive behaviors to prevent development of these behaviors after aversive learning experiences. Future research should therefore examine interventions to decrease the impact of individual risk factors and increase the impact of dampening factors.

However, reliable knowledge about most moderating factors is still scarce. In this regard, we speculate that female sex and gender, adolescent age, adverse life events, high state anxiety, and stress may amplify, while factors such as distress tolerance, sensation seeking, positive affect, social demand, and social incentives may dampen the link between fear learning and defensive behaviors. Future research on these factors is required to provide compelling evidence. In addition, we know little about the relevance of specific moderators for distinct defensive behaviors, for example, whether vulnerability factors such as trait anxiety and intolerance of uncertainty or stress exert comparable effects on defensive reactions, goal-directed actions, and habits. Moreover, it is mostly unclear whether different factors modulate the relationship by enhancing conditioned fear, the expression of defensive behavior, or the link between both. Furthermore, it is mostly unclear whether these moderators affect one or both directions of the bi-directional link between fear learning and defensive behavior. Thus, more research on individual factors is needed. Human aversive conditioning research represent a unique and fruitful tool for this endeavor as it enables disentangling effects on the acquisition of conditioned fear, the degree of instrumental defensive behavior, and the interaction between both.

4.2. Matching interventions to distinct defensive behaviors

A core target of behavioral treatments for anxiety and related disorders is to reduce pathological fear and avoidance. The second line of implications thus concerns the matching of suitable interventions to distinct defensive behaviors. As the learning processes involved in defensive reactions, goal-directed actions, and defensive habits differ, reducing these behaviors should be best achieved by targeting the respective processes. For translational research, it is necessary to map distinct experimental models of change to distinct defensive behaviors and translate these models into distinct clinical interventions (see Fig. 1). In this regard, we suggest that those models and interventions addressing the Pavlovian CS-US association are most relevant for defensive reactions, those aiming at expected outcomes and their values, response-outcome contingency, and CS valence are most relevant for goal-directed defensive actions, and those aiming at habitual responding are most relevant for defensive habits. We propose that matching between interventions and distinct defensive behaviors may inform individualized psychotherapy by identifying and targeting those maladaptive behaviors that are most pronounced in an individual patient.

Pavlovian fear extinction is the most prominent Pavlovian model to inhibit expression of the CS-US association. For example, numerous studies demonstrated that fear extinction training effectively decreases defensive reactions such as the startle response in humans (e.g. Norrholm et al., 2006). We will not discuss potential strategies in more detail, but refer to recent reviews on Pavlovian extinction methods (Dymond, 2019) and how fear extinction can be maximized (Craske et al., 2014; Lebois, Seligowski, Wolff, Hill, & Ressler, 2019; Pittig et al., 2016). Fear extinction training also reduces goal-directed avoidance, but only to a certain degree. Past and recent studies demonstrated that low-cost avoidance is (at least partly) resistant to fear extinction (Pittig, 2019; Pittig & Dehler, 2019; Solomon, Kamin, & Wynne, 1953; Vervliet & Indekeu, 2015). Fear extinction thus only seems to have a limited impact on the instrumentally learned association between the CS+, defensive action, and outcome. Rather than aiming at optimizing the efficacy of Pavlovian procedures, strategies directly targeting instrumental processes may be better suited to downregulate defensive actions.

4.2.1. Targeting goal-directed defensive actions

While most human aversive conditioning research indirectly targets goal-directed avoidance via Pavlovian fear extinction, the direct modulation of goal-directed avoidance is at least equally relevant for clinical translation. In real-life as well as in exposure therapy, refraining from avoidance or safety behavior is a necessary precursor of fear extinction (and not only occurs afterwards as in most human aversive conditioning studies). In other words, before a new learning experience with a feared situation or stimulus can take place, patients need to approach this stimulus or situation. This approach represents an active action selection process and not only passive observation after forced removal of the avoidance response (as in fear extinction models). In treatment and real-life, the option to avoid is usually available, even when the therapist asks the patient to not avoid. Exposure-based treatments thus typically consist of a stepwise process in which strategies to reduce avoidance and safety behaviors precede any actual exposure exercises. In this regard, strategies focusing on factors underlying instrumental learning and expression of goal-directed avoidance, which then modulate fear responses, may be a more valid model than passive Pavlovian extinction alone.

As outlined in the introduction, relevant factors for goal-directed learning are the expected outcomes, the action-outcome contingency, as well as the motivational value of the outcomes. A variety of experimental models and clinical interventions targeting these factors exist. We separate them into two types: 1) Models and interventions targeting the threatening outcome and its contingencies and 2) models and interventions targeting alternative outcomes.

The first type aims to directly target the “aversive component” underlying goal-directed avoidance. Instrumental extinction procedures, for example, include removing the aversive event, making the aversive event ineliminable, or response-independent termination of the aversive event. These experimental procedures reduce goal-directed US-avoidance (as reviewed by Dymond, 2019). However, their premises need to be carefully considered for clinical translation. Some of these procedures aim to change the response-outcome contingency by presenting or terminating the aversive outcome (i.e., the US) independent of the avoidance response. They therefore require strong control over the occurrence of the aversive outcome, which may not always be possible in real-life or treatment. Critically, these strategies require the repeated occurrence of the aversive outcome, which in the clinical context may represent punishment regarding some feared outcomes (e.g., social rejection independent of safety behaviors) and is not possible for others (e.g., heart attack or suffocation in panic disorder). In addition, recent approaches of exposure therapy explicitly focus on the mismatch between expected outcomes and their non-occurrences, thus, enforcing the absence of the aversive outcome (i.e., expectancy violation, e.g., Craske et al., 2014). Finally, removing the aversive event is assumed to reduce goal-directed avoidance by making it unnecessary (Dymond, 2019). As stated above, low-cost avoidance, however, tends to persist after the mere removal of the aversive event (Pittig, 2019; Pittig & Dehler, 2019; Solomon, Richard, Kamin, & Wynne, 1953; Vervliet & Indekeu, 2015). In sum, instrumental extinction procedures change action-outcome contingencies and thereby can reduce goal-directed avoidance, but their clinical translation may be limited and requires further research and refinement.

The scope of clinical interventions targeting threat expectancies already reaches well beyond experimental models in human aversive conditioning research. For example, a wealth of cognitive and metacognitive interventions has been demonstrated to reduce pathological fear and avoidance (e.g., Wells, 1997, 2011). In addition to exposure exercises, threat expectancies can be changed by cognitive restructuring, empirical disputation and reasoning, or behavioral and observational experiments for belief disconfirmation in humans. Considering a reciprocal model for psychotherapy research (see Richter et al., 2017), experimental psychopathology should strive to develop suitable experimental models for strategies already known to be clinically effective to allow for their controlled investigation and optimization. For example, human aversive conditioning research repeatedly showed that fear acquisition and extinction as well as acquisition of defensive actions can be achieved via instructed or observational learning (Cameron et al., 2016; Dunsmoor & Paz, 2015; Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015). Future research should examine the effects of these processes for the extinction of goal-directed avoidance and their validity for respective clinical interventions.

In addition to these interventions targeting contingencies and expectancies, interventions may also target the negative valence of the CS. As mentioned above, the CS+ also acquires a negative valence and may thereby trigger automatic avoidance tendencies and function as a second-order negative outcome, which may motivate CS-avoidance. Reducing the negative valence may thus reduce automatic avoidance tendencies and goal-directed CS-avoidance. Importantly, fear extinction may not (fully) alter the negative valence of the CS+ (e.g., Kerkhof, Vansteenwegen, Baeyens, & Hermans, 2011; Vansteenwegen, Francken, Vervliet, Clercq, & Eelen, 2006, but see Lipp, Oughton, & LeLievre, 2003). In this regard, counterconditioning, US revaluation,[4] and CS revaluation strategies may be better suited (e.g., Dibbets, Lemmens, & Voncken, 2018; Mason & Richardson, 2012). Most research on the impact of these strategies focused on Pavlovian conditioned responses. However, one recent study in children found that counterconditioning (i.e., replacing the US with an appetitive outcome) compared to fear extinction (i.e., no outcome) better reduced goal-directed avoidance in one (i.e., distance a manikin was placed to the CS), but not a second measure of avoidance (i.e., behavioral approach test; Reynolds, Field, & Askew, 2018). US revaluation strategies effectively reduce negative valence of the CS and, for example, include repeated presentation of the US alone to enable US habituation (e.g., Hammerl, Bloch, & Silverthorne, 1997) or more explicit strategies to reduce the aversiveness of the US such as imagery rescripting protocols (see Dibbets et al., 2018). Furthermore, it has recently been demonstrated that CS revaluation by means of presenting positive information linked to the CS+ can also reduce the negative valence of the CS (Luck & Lipp, 2018). To the best of our knowledge, there are no studies examining the effect of these strategies on goal-directed defensive behaviors within an aversive conditioning framework. Thus, more research is needed to examine the impact of changing the negative valence of the CS on goal-directed defensive behaviors.

Fear-opposite action. The second type of interventions aims to decrease goal-directed defensive actions by establishing alternative outcomes for a competing approach behavior. In this regard, these interventions do not directly target the aversive component underlying goal-directed avoidance, but aim at initiating an "opposite action" despite the aversive component. We thus call this line of models and interventions *fear-opposite actions*. Fear-opposite actions account for findings that goal-directed avoidance can easily be reduced by different external moderators (see Dampening factors). In human aversive conditioning, incentives for approaching a feared stimulus have repeatedly been shown to initiate fear-opposite actions. For example, this was demonstrated for tangible and intangible monetary rewards (e.g., Aupperle et al., 2011; Bublatzky, Alpers, & Pittig, 2017; Pittig & Dehler, 2019; Sierra-Mercado et al., 2015; Talmi et al., 2009), positive social stimuli (Pittig, Hengen et al., 2018), and reduced temporal effort (Rattel et al., 2017). Importantly, while these strategies do not directly target fear learning, we recently demonstrated an indirect reduction of conditioned fear responses (Pittig, 2019). Specifically, competing positive outcomes decreased goal-directed US-avoidance, which allowed for Pavlovian fear extinction to take place as soon as the aversive outcome did not occur anymore. Without competing outcomes, US-avoidance persisted in the absence of the aversive outcome, and prohibited Pavlovian extinction. Thus, initiating fear-opposite actions by competing outcomes prevented protection from fear extinction. This highlights that directly targeting goal-directed defensive actions indirectly initiates Pavlovian fear extinction. This stepwise process resembles exposure-based treatments in which strategies to reduce avoidance and safety behaviors precede actual exposure. In this regard, fear-opposite actions resemble clinical strategies in which competing goals, rewards, or values are mapped out to motivate approach of feared situations (such as in Acceptance-Commitment therapy, Hayes, Strosahl, & Wilson, 2003). However, research and experimental models are still scarce. It remains unclear which other processes may initiate fear-opposite action in human aversive conditioning (e.g., social demand) and which individual differences may influence them (e.g., distress tolerance).

4.2.2. Targeting defensive habits

Although considering habits is a somewhat novel approach to the field of aversive conditioning (LeDoux & Daw, 2018), there is a long tradition of targeting habits in behavioral treatments. Traditional habit reversal trainings, for example, involve awareness raising and training of competing responses (Woods & Miltenberger, 1995). Habit reversal trainings are mainly used to treat maladaptive repetitive behaviors such as nail-biting, trichotillomania, or tics (Woods & Miltenberger, 1995). As most instrumental defensive behaviors in patients are more complex, training competing responses may be more relevant for circumscribed behaviors such as compulsive checking. However, we suggest that two interventions already used in behavioral treatments may be beneficial to target defensive habits: awareness raising and stress reduction. Awareness raising may help to revert habitual avoidance to goal-directed control. In the clinical context, this can be achieved with multiple interventions including psychoeducation, the development of disorder and treatment models, or diary methods to monitor behavior in anxiety situations (Thiele, Laireiter, & Baumann, 2002). In addition, recent interventions such as mindfulness may also help to raise awareness about dysfunctional habits (Shapiro & Carlson, 2009). Interestingly, there is a long debate on whether interventions such as relaxation or stress reduction are beneficial for the treatment of anxiety

[4] These strategies are also referred to as "US devaluation". We use the term *revaluation* to minimize confusion with US devaluation used in the context of habits.

disorders (Lilienfeld, 2007; Manzoni, Pagnini, Castelnuovo, & Molinari, 2008). Mapping these interventions to distinct defensive behaviors may help to better understand under which clinical conditions these interventions are useful. For example, applying relaxation during exposure exercises may function as a safety behavior and thereby impede fear extinction learning. As stress presumably shifts the balance between habitual and goal-directed behavior towards habitual behavior, stress reduction, mindfulness, or relaxation may, however, be helpful when applied as separate, stand-alone strategies to target dysfunctional habitual avoidance. Such implications, however, require experimental and clinical investigation.

5. Conclusion and future directions

In the past century, research using Pavlovian human aversive conditioning has greatly expanded our understanding of human functional and dysfunctional fear learning. While research on human instrumental defensive behavior fell out of favor during the last decades, it currently reemerges. Focusing on this resurging research, we highlight a bi-directional relationship between conditioned fear and instrumental defensive behaviors. While acquired fear guides instrumental defensive behaviors via distinct mechanisms (e.g., relief, generalization, PIT), instrumental defensive behaviors may initially reduce fear, but also preserve or even increase fear. Multiple moderating factors either amplify (e.g., trait anxiety, stress) or dampen (e.g., competing outcomes, distress tolerance) this bi-directional link. However, it is still largely unknown how these moderating factors exactly take effect, i.e., whether these factors directly change instrumental defensive behaviors, change conditioned fear and thereby indirectly instrumental defensive behaviors, or moderate the link between both. In this regard, human aversive conditioning paradigms are able to systemically disentangle these different processes, e.g., by comparing the impact of a moderator on Pavlovian and instrumental learning phases. Future studies should thus report associations between a moderating variable with fear responding as well as with defensive behaviors and test for moderator effects.

Moreover, the distinction between different defensive behaviors and matching of these behaviors to distinct experimental models and clinical interventions is useful to advance future experimental and clinical research. For experimental research, traditional models need to be expanded. For example, most human aversive conditioning research examined US-avoidance. While US-avoidance is a proxy of safety behavior in the clinical context (see Introduction), CS-avoidance as a proxy for clinical avoidance has at least equal clinical relevance. Individuals with anxiety disorders oftentimes completely avoid feared stimuli or situations (e.g., not using public transportation, not going to shopping malls). These situations are typically approached during exposure exercises. Yet, there is little research on CS-avoidance and how to overcome it (e.g. Pittig & Dehler, 2019; Pittig, Schulz et al., 2014; Wong & Pittig, n.d.). Thus, future research should also focus on the models, mechanisms, and moderators of CS-avoidance.

In addition, little research has targeted the direct extinction of instrumental defensive behaviors and its generalization. For example, observational and instructed learning models should be investigated alongside interventions that may boost extinction of instrumental defensive behavior. Moreover, avoidance-related PIT effects and their potential moderators should receive more attention (e.g., Lewis, Niznikiewicz, Delamater, & Delgado, 2013). Finally, little is known about defensive habits, their moderating factors, their impact on fear responding, and their clinical relevance. While emerging evidence supports the general role of defensive habits (see Cain, 2019), it is not clear how relevant these habits are in the clinical context. For example, it is unclear to what extant everyday avoidance and safety behaviors actually represent defensive habits that are insensitive to their outcome. Patients may also continuously perform these behaviors with the goal to prevent persistent expectancy of threat, which would rather quantify as repeated goal-directed defensive action. For clinical implications, future research thus needs to examine the relevance of the different defensive behaviors in naturalistic everyday and treatment settings.

For clinical implications, individualized treatments that specifically target a certain type of defensive behavior or moderating factor may improve treatment outcome. As a vision for future research, understanding moderating factors and matching between models and interventions can be combined to optimally inform individualized psychotherapy. For example, while goal-directed avoidance may be decreased by a variety of interventions, social reinforcement may be particularly helpful in individuals who lack social support. Alternatively, exposure techniques may be most helpful to reduce goal-directed avoidance in individuals with amplifying traits known to increase avoidance via enhancing fear responding. In the future, this individualized approach may help to find optimal interventions for individual patients. However, a more comprehensive understanding of the mechanisms, moderators, and clinical translation is required.

Crucially, all clinical implications depend on the clinical validity of the used paradigms. Although the clinical implications are not bound to a specific paradigm, they require experimental models with construct, predictive, and diagnostic validity (see Krypotos et al., 2018). Most human aversive conditioning research focused on low-cost US-avoidance paradigms. These paradigms model avoidance of a single aversive stimulus without any competing outcomes, which would motivate an alternative behavior. In this case, avoidance is an adaptive response, which casts serious doubt on the validity of the paradigm for pathological defensive behaviors. Krypotos et al. (2018) pointed out that there is currently no study to verify the diagnostic validity of this paradigm for anxiety or related disorders. In addition, our discussion of external dampening factors highlight that avoidance may drastically change by introducing alternative outcomes. Importantly, we recently demonstrated that individuals with high compared to low levels of trait anxiety show elevated costly avoidance, but not low-cost avoidance (Pittig & Scherbaum, 2019). These findings challenge the validity of low-cost avoidance for anxious psychopathology. To inform treatment and prevention strategies, research needs to verify the diagnostic validity of traditional paradigms or switch towards more suitable paradigms (e.g., costly avoidance). Validating currently used experimental models thus represents a crucial gap of current research.

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