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The role of associative fear and avoidance learning in anxiety disorders: Gaps and directions for future research

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ABSTRACT

Anxiety disorders are the most common mental disorders and are often chronic and disabling. Although exposure-based treatments are effective, a substantial number of individuals fail to fully remit or experience a return of symptoms after treatment. Understanding the critical processes underlying the development and treatment of anxiety disorders will help identify individuals at risk and optimize treatments. Aversive associative learning offers explanatory pathways through which fear and anxiety emerge, spread, persist, and resurge. This narrative review examines the advances made in our understanding of associative fear and avoidance learning in anxiety disorders. Overall, the extant literature supports a key role of aversive associative learning in the development and treatment of anxiety disorders. However, research targeting specific mechanisms such as extinction generalization and avoidance, the fragility of extinction, and moderating influences of individual differences pertinent to anxiety disorders (e.g., age, sex, depression) is needed. We discuss the need for more ecological valid and complex paradigms to model ambiguity and conflict as well as for clinical translation studies to optimize treatment.

1. Introduction

Aversive associative learning has played a major role in explaining the development and treatment of anxiety disorders as well as related disorders such as posttraumatic stress disorder (PTSD) or obsessive-compulsive disorder (OCD). However, despite the significant advances made, there are critical processes involved in the emergence, maintenance, and treatment of these disorders that are not understood. Such areas, for example, include sex differences in the prevalence of anxiety disorders, developmental pathways, the effect of comorbidity with depression, the role of avoidance, and ways of overcoming the fragility of extinction and enhancing the long-term effects of exposure-based treatments. The present review critically examines advances made to date, the gaps in the existing literature, and directions for future research, with the ultimate aim to improve prevention efforts and treatment effectiveness.

Fear, anxiety, and avoidance behavior are evolutionarily adaptive processes that are commonly experienced in everyday life. However, individuals with anxiety disorders are excessively fearful, anxious, or avoidant of perceived threats in their environment (e.g., social situations, unfamiliar locations) or within themselves (e.g., unusual bodily sensations, thoughts and mental images). The response to these stimuli is out of proportion to the actual threat or danger posed and often generalizes to a wide range of related stimuli. Excessive fear and anxiety in individuals with anxiety disorders is typically accompanied by excessive avoidance behaviors, which range from complete refusal to enter fear-relevant situations to more subtle reliance on objects, behaviors, or people to cope with subjective expectations of threat.

Anxiety disorders as a group represent the most common class of mental disorders (Kessler et al., 2010). A systematic review of prevalence studies across 44 countries estimates the current global prevalence at 7.3% (95% CI 4.8–10.9%), suggesting that about one in 14 people around the world at any given time are affected by a clinically significant anxiety disorder (Baxter et al., 2013). Furthermore, about one in nine (11.6%, 95% CI 7.6–17.7%) will experience an anxiety disorder in a given year (Baxter et al., 2013). Worldwide, middle-aged adults (35–54 years) are 20% more likely to have an anxiety disorder compared to older adults (55 years plus; Baxter et al., 2013). For specific anxiety disorders, most separation anxiety disorders and specific phobias develop in childhood and most social anxiety disorders in adolescence or early adulthood. The onset for panic disorder, agoraphobia, and generalized anxiety disorder is typically later and with

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greater dispersion (Kessler et al., 2010). Prospective studies of children and adolescents often yield even lower ages of onset (Beesdo-Baum and Knappe, 2012). Moreover, women are twice as likely to have an anxiety disorder as men (McLean et al., 2011), but sex differences remain poorly understood. These epidemiological findings highlight the importance to account for individual differences such as age or sex in the etiology of anxiety disorders. Finally, anxiety disorders frequently co-occur with depression (Kessler et al., 2005). In fact, anxiety disorders are one of the strongest known risk factors for and precursors of depression and linked to a more malignant course of depression (Beesdo et al., 2007; Meier et al., 2015). Models of anxiety disorders and their treatment should thus take into account the effects of co-occurring depression.

If untreated, anxiety disorders tend to be chronic, with a waxing and waning pattern of recurrence across the lifetime (Bruce et al., 2005; Kessler et al., 2010). Anxiety disorders are not only persistent, but also pervasive, with fear generalizing to broad array of stimuli (Dymond et al., 2015). The breadth of fear and avoidance contributes to functional impairments, with anxiety disorders being the sixth leading cause of disability in high and low income countries (Baxter et al., 2014). Impairment and disability may be greater for women than men with anxiety disorders (McLean et al., 2011). Etiological models therefore must be able to account for their persistence and spread.

Given the high prevalence, burden, and chronicity of anxiety disorders, the development and improvement of effective treatments is vital. Several pharmacological interventions are approved for anxiety disorders and demonstrate pre-to-post effectiveness (Bandelow et al., 2015), but many individuals do not remit, are unwilling to tolerate side effects, and/or prefer non-medication treatment options. Cognitive behavioral therapies for anxiety disorders, most of which incorporate exposure-based interventions, are highly effective. For example, relative to waitlist or passive control conditions, the effect size in adult samples is medium to large (Hedges g = 0.73; 95% CI = 0.56–0.90; Hofmann and Smits, 2008). Corresponding effects for childhood samples are large as well (SMD = −0.98; 95% CI = −1.21 to 0.74; James et al., 2013) and medium to large for late life samples (Hedges g = −0.66, 95% CI = −0.94 to −0.38; Gould et al., 2012). Direct comparisons to active treatment conditions are more limited but findings indicate benefits with medium effect sizes for exposure-based cognitive-behavioral therapies over other types of therapies such as psychodynamic treatments (Cohen's d = 0.43; 95% CI = 0.14–.72; Tolin, 2010). As a result, exposure-based cognitive-behavioral therapies are a first line treatment in many international treatment guidelines for anxiety disorders.

Despite the high effectiveness of exposure-based cognitive-behavioral therapies, a number of essential shortcomings have been identified. First, a substantial number of individuals (11–27%) refuse to begin cognitive behavioral therapies when offered (Fernandez et al., 2015; Garcia-Palacios et al., 2007). Second, another substantial number (15–52%) drops out after beginning treatment (Fernandez et al., 2015; Haby et al., 2006). Third, the rate of clinically significant response to cognitive behavioral treatments is much less than ideal, averaging 50–60% (Loerinc et al., 2015; Rapee et al., 2009). And finally, individuals may exhibit a return of fear or full relapse following successful treatment (Craske and Mystkowski, 1999; Ginsburg et al., 2014). Short-term and long-term treatment effectiveness is likely to be improved by a better understanding of the critical pathways through which anxiety disorders emerge, spread and persist, and the moderating effects of age, sex, and comorbidity with depression. With this information at hand, we will be positioned to develop more targeted prevention and treatment efforts.

1.1. The role of associative learning processes in anxiety disorders

Associative learning refers to the process by which relationships among various stimuli, behaviors, and outcomes are learned (Rescorla, 1988). This learning involves representations and memories necessary for adapting to our environment and guides our understanding of what is threatening and what is safe; what is rewarding and what is not; when to approach and when to avoid; and when to repeat an action and when not to. For anxiety disorders, aversive associative learning (i.e., associative learning related to aversive stimuli or outcomes) is assumed to be a core underlying learning process. Aversive associative learning comprises different processes including learning regarding predictive relationships among stimuli and an aversive outcome (aversive Pavlovian learning), as well as associations among a response and an outcome (aversive instrumental or operant learning such as avoidance learning). For anxiety disorders, the validity of aversive associative learning as an underlying learning process and experimental model has been well documented and helps explain how maladaptive fear, anxiety, and avoidance are learned and maintained (Arnaudova et al., 2017; Krypotos et al., 2015; Scheveneels et al., 2016; Vervliet and Raes, 2013).

Most current research focuses on the role of aversive Pavlovian learning. Experimental procedures of aversive Pavlovian learning are known as fear or threat conditioning, which are overarching terms including procedures of fear acquisition, extinction, and return of fear (see Lonsdorf et al., 2017). In Pavlovian fear acquisition, a former neutral stimulus elicits a fear response due to its predictive relationship with an innately aversive stimulus (the aversive unconditional stimulus or US). Likewise, the reduction of conditioned fear when the feared stimulus is presented in the absence of an aversive stimulus (i.e., during fear extinction training) is seen as laboratory proxy for fear reduction during exposure treatment. Combined, these similarities between experimental and clinical phenomena provide face validity for the experimental model of fear conditioning (Scheveneels et al., 2016; Vervliet and Raes, 2013). The underlying associative learning processes are also assumed to be crucial mechanisms in the etiology of anxiety disorders (offering *construct validity*). For example, deficits in aversive Pavlovian learning predict both the emergence of post-traumatic stress disorder (e.g., Lommen et al., 2013), and the persistence of symptoms (Sijbrandij et al., 2013). Moreover, changes in aversive Pavlovian learning, and its neural substrates, following exposure therapy co-vary with symptom improvement (Helpman et al., 2016; Kircher et al., 2013; Lueken et al., 2013). Recent studies also provided first evidence that individual differences in aversive Pavlovian learning predict responses to exposure-based treatments (Ball et al., 2017; Forcadell et al., 2017; Waters and Pine, 2016). Although additional processes contribute to successful exposure therapy, these results offer *predictive validity* for aversive associative learning as one underlying mechanism of exposure.

Finally, individuals with anxiety disorders show distinct deficits in aversive Pavlovian learning models compared to healthy controls (*diagnostic validity*; e.g., Duits et al., 2015; Jovanovic et al., 2012; Lissek et al., 2005). Whereas this research mostly targeted the validity of aversive Pavlovian learning for anxiety disorders, research on the validity of avoidance learning, which also involves instrumental and other learning processes (see 5.), is still scarce (see also Scheveneels et al., 2016; Vervliet and Raes, 2013).

Treatments for anxiety disorders, beginning with Wolpe's method of systematic desensitization (Wolpe, 1958) and extending to current day models of exposure therapy, were directly derived from associative learning models, in particular, the processes of fear extinction. However, treatment development has been stymied by lack of translation of advances in research on fear and avoidance learning to treatment and by the failure of basic science to fully model the complexity and essential features of anxiety disorders and naturalistic treatment conditions (see Craske et al., 2014, 2008a; Pittig et al., 2016; Richter et al., 2017). Thus, although aversive associative learning is perhaps one of the best examples of a science-driven model for understanding and treating psychopathology (Holmes et al., 2014), there is a strong need for more reciprocal and iterative investigations involving both basic and clinical science to advance our models and methods of treating

anxiety disorders and related conditions (see also Richter et al., 2017).

Recent reviews on aversive associative learning focused on distinct mechanisms such as fear acquisition, generalization, extinction, and return of fear (e.g., Dymond et al., 2015; Haaker et al., 2014; Hermans et al., 2006; Vervliet et al., 2013a, 2013b), their neural substrates (e.g., Etkin and Wager, 2007; Fullana et al., 2016; Greco and Liberzon, 2016; LeDoux and Pine, 2016; Maren, 2001; Maren and Holmes, 2016; Mechias et al., 2010; Medina et al., 2002; Milad and Quirk, 2012; Sehlmeyer et al., 2009), and the general role of aversive Pavlovian learning for anxiety disorders (e.g., Craske et al., 2014, 2006; Duits et al., 2015; Kindt, 2014; Lissek et al., 2005; Mineka and Zinbarg, 2006; Pittig et al., 2016). In addition, recent reviews also focused on methodological issues of the corresponding experimental models (e.g., Beckers et al., 2013; Lonsdorf et al., 2017) and general overviews on individuals differences within these models (e.g., Lonsdorf and Merz, 2017). Few of these reviews have focused on clinical implications and most exclusively focused on aversive Pavlovian learning. Although avoidance is also a crucial mechanism for anxiety disorders, comprehensive overviews of avoidance learning are scarce.

To further advance our understanding of the involvement of aversive associative learning processes for anxiety and related disorders, this narrative review focused on the clinical relevance of associative learning processes involved in the acquisition, generalization, persistence, and return of fear and avoidance for the development, prevention, and treatment of anxiety and related disorders (see Fig. 1). To this regard, the present review aimed at:

1 Reviewing extant evidence for alterations in distinct mechanisms of aversive associative learning in individuals with anxiety disorders or at-risk for anxiety disorders.
2 Highlighting the impact of individual differences that are pertinent to the etiology and treatment of anxiety disorders, especially sex and age differences, developmental issues, and comorbid symptoms of depression.
3 Providing an overview of the emerging research on avoidance learning and its clinical relevance.

In the following sections, we briefly describe associative learning processes and corresponding experimental models involved in the acquisition, generalization, persistence, and return of fear and avoidance. For each process, we then address the question whether anxious individuals show imbalances in the specific process and highlight the individual differences pertinent to anxiety disorders (i.e., sex, age, comorbid depression). In addition, we highlight methodological issues (“*Paradigms*”) and important gaps and future research directions relevant to each mechanism. In addition to the DSM-5 anxiety disorders (APA, 2013), the review also considers OCD and PTSD as disorders that have a strong fear-based component and associative learning theory-informed etiological and treatment models.

2. Fear acquisition

2.1. Mechanisms of fear acquisition

Within an associative learning framework, fear acquisition refers to the process of acquiring fear as a result of the repeated pairing of a stimulus with an aversive US, which is referred to as fear acquisition training (see Lonsdorf et al., 2017). In general, three processes of fear acquisition are differentiated: i) learning by direct experience, ii) observational or vicarious learning, and iii) informational transmission or instructed learning (Olsson and Phelps, 2007; Rachman, 1977). It is important to note that despite these seemingly disparate processes of fear acquisition, all of these processes recruit similar neural structures, proceed via shared mechanisms (e.g., error correction) and are therefore united under the concept of aversive Pavlovian learning (Lindström et al., 2018; Lovibond, 2003; Meffert et al., 2015; Olsson and Phelps, 2007, 2004; Sevenster et al., 2012). Aversive Pavlovian learning simply refers to the process through which relations among stimuli in one’s environment are learned (Rescorla, 1988). Thus, research including all three types of fear acquisition supports the associative development of anxiety disorders. Detailed understanding of this fear acquisition processes and potential modulating factors may thus help to identify individuals at risks for anxiety disorders and prevent the manifestations of these disorders.

Probably the most prominent pathway of fear acquisition is by direct experience with an aversive event (e.g., being bitten by a dog or being ridiculed at a social event). Aversive associative learning models are frequently used as laboratory analogues for such real-life experiences by pairing a to-be-conditioned stimulus with direct experience of an aversive US (e.g., Lonsdorf et al., 2017; Mineka and Zinbarg, 2006). The ethical limits placed upon the intensity of the US in the laboratory bring into question the degree to which those procedures adequately model real-life aversive learning. However, it has been suggested that fear-relevant CSs may be able to activate fear-relevant networks in the brain to the same degree as a highly aversive US (Mineka and Öhman, 2002). Furthermore, animal studies often involve more intense USs than can be used in human studies. Moreover, naturally occurring examples of direct aversive experiences that induce long-lasting fear and anxiety in humans are plentiful, for example, post-traumatic stress following sexual and other forms of abuse, combat and violence, social anxiety following social ridicule or humiliation, and agoraphobic anxiety following unexpected panic attacks in certain situations. Thus, fear acquisition training represents a valid experimental model with high translational value (Scheveneels et al., 2016; Vervliet and Raes, 2013).

In the simplest experimental model of fear acquisition (i.e., single

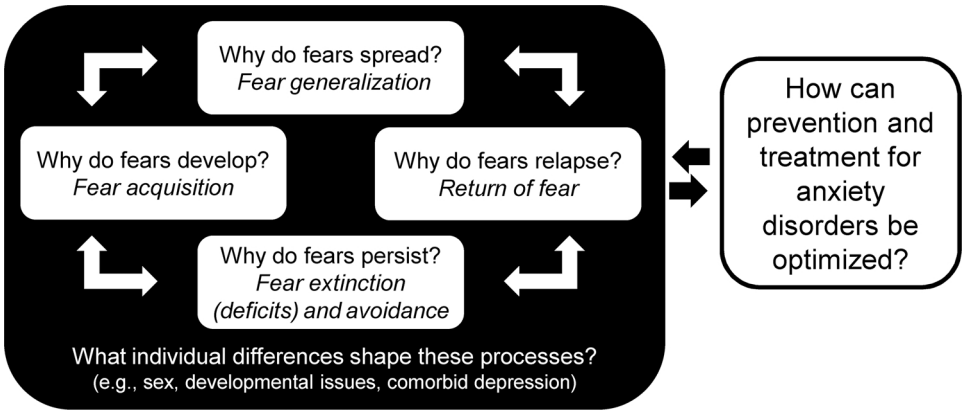

Fig. 1. Schematic representation of essential research questions to address the development, maintenance, and treatment of maladaptive fear and anxiety.

cue acquisition training), individuals observe the repeated pairing of a single neutral stimulus (NS) with an aversive US (e.g., an aversive electrical stimulation, loud noise, or aversive air puff). The former neutral stimulus thereby becomes a conditional stimulus that signals the US (CS+) and elicits conditional fear responses (CR). In differential acquisition trainings, another neutral stimulus is presented equally often but is never paired with the US, turning this stimulus into a conditional safety stimulus (CS−), which signals the absence of the US. During acquisition, successful learning of conditional fear is indicated by elevated fear responses towards the CS+ compared to the CS-. These fear responses are typically measured across subjective-verbal, psychophysiological and behavioral read-out measures (for a detailed overview see Lonsdorf et al., 2017). On the subjective-verbal level, expectancy ratings (i.e., the self-reported probability of an upcoming US) are assessed to measure cognitive contingency awareness. In addition, ratings of valence, fearfulness, or arousal towards the CSs indicate affective components of subjective-verbal responses to fear acquisition training. On the physiological level, successful fear acquisition is observed in distinct responses in the peripheral and central nervous system. Peripheral responses are typically assessed by measuring skin conductance responses (SCRs), the potentiation of the eye blink startle response, or differential heart rate responses. SCR represents a short-term, phasic change of the skins' conductance (i.e., by sweating) in response to the onset of a stimulus and represents autonomic nervous system activity (Boucsein et al., 2012). Elevated SCRs towards the CS+ following acquisition training signal successful fear acquisition. Likewise, elevated startle responses towards the CS+ signal fear acquisition, as the startle reflex is potentiated in the presence of negative stimuli (Davis et al., 1993; Grillon and Baas, 2003). On the neural level, blood oxygen-level dependent (BOLD) responses to the CS+ compared to the CS− are most commonly measured in human functional magnetic resonance imaging (fMRI) studies.

Briefly, these fMRI studies provide evidence for distinct but highly interconnected brain regions in fear acquisition including the amygdala, the anterior insula cortex (AIC), the dorsal anterior cingulate cortex (dACC), and the hippocampus (for details see Etkin and Wager, 2007; Fullana et al., 2016; Greco and Liberzon, 2016; Mechias et al., 2010; Sehlmeyer et al., 2009). The most recent meta-analysis, however, showed no amygdala activation in human fear acquisition (Fullana et al., 2016). In line with this finding, LeDoux and Pine (2016) have challenged the view of a central fear network centered on the amygdala in humans. In contrast, they proposed a two-system framework, in which a subcortical circuit including the amygdala mainly guides defensive behaviors and physiological responses to threat, whereas the conscious experience of fear is associated with different neural circuits to which the amygdala provides only indirect input (LeDoux and Pine, 2016). Although this framework may account for the mixed findings of amygdala activation, it has been criticized (Fanselow and Pennington, 2018). In addition, the lack of amygdala activity in the recent meta-analysis may be linked to specific methodological features (e.g., less sensitive whole brain analyses or categorical comparison of CS+ vs. CS−; see Sehlmeyer et al., 2009). Irrespective of precise neural network involved, findings on all the above mentioned levels of emotional responding verify the acquisition of fear and anxiety by means of direct aversive experience.

Besides such direct experience, it has been long recognized that fear and anxiety can be acquired by vicarious experience (Rachman, 1977). Vicarious fear acquisition occurs through observing others experiencing an aversive event or extreme fear. Mineka et al. provided rigorous experimental evidence of vicarious fear acquisition in rhesus monkeys (e.g., Cook and Mineka, 1990, 1989; Mineka et al., 1984; Mineka and Cook, 1993, 1988). Laboratory-reared young adult monkeys that were not previously exposed to snakes observed unrelated, wild-reared monkeys react fearfully in the presence of live and toy snakes and non-fearfully in the presence of neutral objects. The majority showed rapid acquisition of intense fear of snakes but not of the neutral objects. This fear was nearly as strong as the fear usually observed in wild monkeys and persisted for at least three months. Mineka and Cook (1993) argued that processes involved in vicarious acquisition are very similar to those involved fear acquisition by direct experience: the observer monkey's behavior in the presence of the snake (CS) may be seen as a conditional response (CR) to the observed pairing of the snake and the model monkey's display of fear (US). Since that time, a number of studies have demonstrated that youths (as young as 12–24 months old) display fear-related behaviours (e.g., fearful facial expressions and behavioural avoidance) to neutral objects after observing fear reactions by their mothers to those objects. Thus, past research verified the development of maladaptive fear and anxiety also occurs by means of observational learning, although the durability of these effects needs to be further investigated (de Rosnay et al., 2006; Dubi et al., 2008; Gerull and Rapee, 2002).

A third mechanism of fear acquisition is informational transmission (Rachman, 1977). Informational transmission refers to conveyance of threatening information about specific objects or situations, as occurs with parental warnings or media reports about dangers inherent in specific situations. Indeed, children can learn fearful behaviour following verbal transmission of threat about novel objects (Field, 2006; Field and Lawson, 2003), although again the persistence of such learning is unclear. In laboratory models, fear acquisition by informational transmission has been demonstrated using threat instruction paradigms, in which participants are merely instructed that a certain CS may be followed by an aversive event (e.g., Bublatzky et al., 2017, 2014; Olsson and Phelps, 2007; Schmitz and Grillon, 2012). Thus, informational transmission can also lead to the development of maladaptive fear and anxiety.

Taken together, research incorporating different laboratory models and multilevel emotional responses provided comprehensive evidence that Pavlovian fear acquisition can be modeled under experimental conditions. These experimental models have frequently been used to investigate whether individual differences in Pavlovian fear acquisition may contribute to the development of anxiety disorders.

2.2. Pathways by which fears may be more readily acquired

Although fear acquisition represents an adaptive process, individual differences that negatively impact Pavlovian processes may result in stronger or more rapid fear acquisition and, therefore, contribute to the genesis of pathological fear and anxiety. In support, individuals with anxiety disorders show a proneness to acquire associative fear more strongly than healthy individuals, at least within single cue acquisition trainings (Lissek et al., 2005). This heightened responding to the CS+ includes self-reported US expectancy, skin conductance, and patterns of neural activation. In particular, elevated amygdala activation has been observed during fear acquisition in individuals with anxiety disorder relative to healthy controls (Bremner et al., 2005; Milad et al., 2009b; Schneider et al., 1999; Veit et al., 2002). Since these studies are cross-sectional, the direction of causality is unknown – do individual differences elevate fear acquisition that in turn contributes to anxiety disorders, or do anxiety disorders contribute to elevated fear acquisition? Support for the former direction of causality may be drawn from investigating individual differences that constitute a risk for developing an anxiety disorder before its actual manifestation. For example, youth who were at risk for anxiety disorders by virtue of parental anxiety, but who themselves did not experience anxiety disorders, show elevated fear acquisition (Craske et al., 2008b). In addition to the question of causality, elevated fear acquisition in individuals with anxiety disorders was not supported in more complex fear acquisition paradigms (Lissek et al., 2005; Duits et al., 2015). Thus, a critical next step is identifying the key factors that may contribute to individual differences in fear acquisition and how these factors relate to the development of anxiety disorders. In this line, multiple factors such as personality traits, genetic differences, latent inhibition experience as well as sex and age

differences have been targeted.

2.2.1. Personality traits

Personality traits such as high trait anxiety or the general proneness to negative affect (i.e., neuroticism) have been proposed to strengthen fear acquisition and thereby may represent a risk factor for developing anxiety disorders (e.g., Mineka and Zinbarg, 2006; Zinbarg et al., 2016). In support, some studies reported elevated fear acquisition in individuals with high levels of trait anxiety or neuroticism (e.g., Hooker et al., 2008; Jackson et al., 2006). In addition, elevated amygdala activation during fear acquisition training has been observed in individuals with high trait anxious (Indovina et al., 2011). However, extant data regarding the relationship between trait anxiety or neuroticism and a susceptibility to fear acquisition are inconsistent, with a large number of studies failing to demonstrate elevated fear acquisition in higher levels of trait anxiety or neuroticism (e.g., Barrett and Armony, 2009; Haddad et al., 2015; Otto et al., 2007; Pittig et al., 2014c; Sehlmeyer et al., 2011; Torrents-Rodas et al., 2013; Tzschoppe et al., 2014). The link between high trait anxiety or neuroticism and elevated fear acquisition thus seems to depend on the specific outcome measure and methodological differences in experimental designs (for a review see Lonsdorf and Merz, 2017). For example, Lonsdorf and Merz (2017) suggested that trait anxiety may be linked to elevated fear acquisition to the CS+ in unambiguous single cue paradigms, but more strongly to responses to safety stimuli and contexts in more ambiguous designs. This process of elevated responses to safety signals may still be indicative of deficient aversive Pavlovian learning and contribute to psychopathology via mechanisms such as enhanced fear generalization as described below (see Section 3).

2.2.2. Genetic differences

Another individual difference that may contribute to a susceptibility for fear acquisition may be found in genetic differences. There has been some, albeit limited, investigation of genetic contributions to fear acquisition. In a twin sample, fear acquisition was estimated to be 35–45% heritable (Hettema et al., 2003). Initial work has implicated a variety of genetic and epigenetic factors in the acquisition of fear memory. Genetic variations in brain-derived neurotrophic factor (BDNF), which is important for synaptic plasticity and long-term memory formation, and the serotonin transporter gene 5-HTTLPR, which is associated with amygdala reactivity, affect fear learning (Klucken et al., 2015; Lonsdorf et al., 2015a; Rattiner et al., 2004; Wendt et al., 2015). These findings on the heritability of fear acquisition are clearly in need of replication and extension. For example, although genetic variations may confer vulnerability to fear acquisition, epigenetic processes (e.g., histone acetylation, methylation) that affect gene expression and transcription are likely also important (Kwapis and Wood, 2014; Sharma et al., 2016).

2.2.3. Latent inhibition experience

An individual difference that may decrease fear acquisition is previous experience with the to-be-conditioned stimulus. The concept of "latent inhibition" refers to prior exposure to a CS, before it is ever paired with an US, attenuating subsequent fear acquisition (when the CS is paired with the US). Initial accounts of latent inhibition emphasized a loss of salience or associability of the CS because it previously had no predictive value (Mackintosh, 1983). Later accounts posit that pre-exposure to a CS results in an initially learned CS-noUS association, which exerts an inhibitory effect on the expression of the subsequently learned CS-US association (Bouton, 1993; Vervliet, 2013). Like fear acquisition, latent inhibition can occur vicariously, by informational transmission as well as through direct experience. For example, prior direct experience of the future CS+ typically slows fear acquisition in humans (e.g., Vervliet, 2013). Mineka and Cook (1986) found that prior vicarious exposure to a monkey behaving non-fearfully attenuated the development of fear when monkeys subsequently observed a fearful monkey in the presence of a snake. A similar immunization effect has been demonstrated in human fear learning (Golkar and Olsson, 2016).

Latent inhibition may also offer some explanation for the role of parenting in anxiety disorders. A number of studies have shown that parents of anxious children are more likely to engage in overly intrusive, overprotecting, or controlling behaviors (see Rapee et al., 2009). Conceivably, one of the consequences of overly protective parenting is restriction of childhood experiences that could essentially serve as a form of latent inhibition that buffers against the later development of fears. For example, by preventing children from engaging in sports such as swimming or staying with friends overnight, subsequent negative experiences in water or when away from home are less 'buffered', leading to more easily acquired fear acquisition. Of course, many parents of anxious children are themselves anxious, and likely to provide vicarious and informational transmission of fears as well. Thus, future research is needed to disentangle the effect of missing latent inhibition experience and vicarious and informational transmission. Either way, recognition of the role of latent inhibition for prevention efforts suggests that individuals at risk for an anxiety disorder may especially benefit from encouragement to engage in a wide range of experiences that could buffer subsequent fear acquisition (i.e., via parent training). Indeed, encouragement for approach behaviors of this kind is a typical component of prevention programs for youth (e.g., Rapee, 2013).

2.3. Sex differences

Women are twice as likely to have an anxiety disorder as men (e.g., McLean et al., 2011). Different factors that have been linked to female sex and elevated fear acquisition may help to explain these sex differences. First, females score higher on measures of neuroticism than males (e.g., del Barrio et al., 1997; McCrae et al., 2002) and there is some evidence, albeit mixed, indicating that neuroticism elevates fear acquisition (see 2.2.1). Second, a concept that is highly related to neuroticism is worry, or the tendency to perseverate upon future negative possibilities. Females score significantly higher on worry scales than males (Borkovec et al., 1983; Robichaud et al., 2003). Worry may inflate the aversiveness of the US following fear acquisition, leading to an increasing or persistent fear response over time without further direct experience of the US (Davey, 1995; Jones and Davey, 1990). In addition, worry entails repeated mental rehearsal (e.g., rehearsing the CS-US relationship), which has been found to strengthen memory consolidation and fear acquisition (Joos et al., 2012; Meeter and Murre, 2004). The elevated tendency to worry in females may, therefore, be a contributing factor to sex differences in fear acquisition. Third, there is some evidence that over-intrusive parenting is more common with female than male anxious offspring (Krohne and Hock, 1991). Thus, immunization through latent inhibition may be less likely in anxious girls than anxious boys, although research on this association is still missing.

For these reasons, one might speculate that females are more likely to acquire conditional fears than males. However, empirical investigations yielded mixed results. Higher rates of fear acquisition have been found for females in several adult samples (e.g., Guimarães et al., 1991; Inslicht et al., 2013; Lebron-Milad et al., 2012; Lonsdorf et al., 2015b). In contrast, other studies reported elevated fear acquisition in males (e.g., Graham et al., 1966; Milad et al., 2006) or found no sex differences (e.g., Elder et al., 1979; Fredrikson et al., 1976). Mixed results may depend on the specific outcome measure, since women were found to report higher subjective distress but not greater physiological fear acquisition than men (Lonsdorf et al., 2015b). Yet, a recent meta-analysis that included self-report and physiological measures failed to show any significant differences in fear acquisition between males and females (Duits et al., 2015). Thus, additional moderator variables need to be considered. For example, attention has been given to hormonal status, suggesting that elevations in fear acquisition may coincide with

hormonal fluctuations (Hwang et al., 2015; Merz et al., 2012a). However, the findings remain elusive and much more work is needed. So far, there is little compelling evidence that sex differences in associative fear acquisition can explain the different prevalence rates between females and males.

2.4. Developmental issues

Children and adolescents often acquire fear by means of associative fear learning (Schiele et al., 2016; Shechner et al., 2014) and fear onset is often during childhood and adolescence. Thus, age-related differences in fear acquisition may help to explain developmental differences in anxiety disorders. In support, older children showed elevated fear acquisition compared to younger children (6–8 years > 3–5 years; Gao et al., 2010; 11–13 years > 8–10 years; Glenn et al., 2012). Futhermore, relative to adults, adolescents (10–17 years) showed elevated fear acquisition, including stronger SCRs for a CS+ and CS− and increased self-reported fear for the CS- (Lau et al., 2011). Such elevated fear acquisition in comparison to adults was not found in younger children (Schiele et al., 2016). Moreover, a positive correlation between age and neural activation to the CS+ has been found in 12–17 year old adolescents (Haddad et al., 2015), whereas no age-related differences in fear acquisition in terms of SCRs and expectancy ratings seem to occur in 5–10 year old children (Michalska et al., 2016). These findings may suggest a non-linear relationship between age and the strength of fear acquisition, with adolescence being a particularly vulnerable developmental stage. On the other hand, others have reported no differences in fear acquisition between adults and adolescents (Waters et al., 2017). The contradictory findings may be linked to methodological differences in developmental studies on fear learning (Shechner et al., 2014) and thus future research incorporating the same paradigms across a wide age range is required for comprehensive analyses of vulnerable developmental stage for fear acquisition.

2.5. Effect of depression

Data regarding fear acquisition as a function of depression is sparse. Whereas depressed individuals showed enhanced fear acquisition (SCRs) compared to non-depressed healthy controls in one study (Nissen et al., 2010), another study failed to replicate these findings (Kuhn et al., 2014). To the best of our knowledge, no controlled studies have directly compared individuals with anxiety disorders with and without comorbid depression in terms of fear acquisition. Given the high comorbidity of anxiety and depression, corresponding studies are urgently needed.

2.6. Paradigms

As indicated by Beckers et al. (2013), our methods may not fully capture the complexity of human fear acquisition. This may be particularly true for single cue paradigms. These paradigms represent an unambiguous “strong situation” (Lissek et al., 2006), which limits inter-individual variability in responding (i.e., ceiling effects). In other words, if only a single stimulus that precisely predicts the upcoming occurrence of a negative event is present, almost everyone will acquire strong fear. Paradigms with more uncertainty may highlight differences between anxious and nonanxious-prone individuals. Uncertain or “weak situation” paradigms include inhibitory/differential conditioning, stimulus competition, or occasion-setting paradigms (see Boddez et al., 2014). In addition, context conditioning may further increase the ecological validity of laboratory models, especially when using virtual reality to model complex everyday situations (e.g., Ewald et al., 2014; Glotzbach-Schoon et al., 2013; Grillon et al., 2006; Maren et al., 2013; Shiban et al., 2015). Future research should therefore utilize paradigms that involve less certainty or contextual conditioning to mimic ecologically valid environments of fear acquisition.

2.7. Summary: Fear acquisition

Aversive Pavlovian learning represents an important process through which fear may be acquired. Although there is some evidence that anxious individuals demonstrate stronger fear acquisition compared to healthy controls, this evidence is inconsistent and limited to single cue acquisition paradigms (Lissek et al., 2005, Duits et al., 2015). One may thus argue that elevated fear acquisition is not a central mechanism underlying the development of anxiety disorders in some but not other individuals. However, the precise mechanisms responsible for individual differences clearly require further explication. For example, although personality factors (such as neuroticism) have been shown to relate to stronger fear acquisition in some studies, the results are inconsistent. Fewer “latent inhibition” experiences and the tendency to mentally rehearse the CS-US relationship (e.g., through worry) may both contribute to elevated fear acquisition, although there is a dearth of research examining these factors in anxious and at-risk individuals. Similarly, genetic and epigenetic processes that affect long-term memory formation could contribute to individual differences in the acquisition of fear, although there is a need for more large-scale research in this area. In addition, it will be important for future studies to employ more nuanced fear acquisition paradigms (e.g., uncertain or “weak situations”) to elucidate the effect of a given risk factor on the strength and speed of fear acquisition. Finally, there is a need for studies that examine multiple potential risk factors, as these processes likely interact. Once replicable risk factors are identified, prevention efforts can be best targeted at those factors that are most malleable or confer the greatest risk.

3. Fear generalization

Not only do individual differences exist in terms of the strength of fear responding following aversive events, but also in terms of the extent to which fears generalize following such learning experience. In this regard, similar levels of initial fear acquisition may result in different levels of long-term fear expression as some individuals generalize fear to a wider range of stimuli and situations and others do not. Wide fear generalization is assumed to be a hallmark feature of anxiety disorders (Dymond et al., 2015). The process of fear generalization in and of itself is adaptive, since it is sensible to fear harm in situations that resemble the original situation associated with an aversive stimulus. However, there is an important balance between adaptive generalization and excessive generalization in which ostensibly safe situations and objects are needlessly feared.

3.1. Mechanisms of fear generalization

Fear generalization may result from a number of factors, perceptual as well as non-perceptual (see Dymond et al., 2015). Most is known about perceptual fear generalization, in which stimuli that are neutral but *perceptually similar* to conditional fear stimuli (e.g., size; colour) activate fear responses proportionately to the degree of similarity (Andreatta et al., 2015; Bennett et al., 2015; Haddad et al., 2013, 2012, Lissek et al., 2014a, 2008). In categorical generalization, stimuli may become conditional because they are *categorically related* to a CS even though perceptually distinct (Bennett et al., 2015; Dunsmoor et al., 2012; Hermans et al., 2013). Categorical generalization is presumed to involve conceptual knowledge of known objects that belong to the same category to appraise likely threat (Dymond et al., 2015). For example, fear may generalize to older men following a physical assault from an older male perpetrator, despite perceptual differences between these men. Categorical generalization is enhanced when the CS is a *typical* member of a category rather than an atypical one (Dunsmoor and Murphy, 2014). For example, social rejection from someone representative of one’s peer group may result in more social anxiety at school than when rejected by someone older. Fear may also generalize

between stimuli that are semantically related, for example, words that share a similar meaning (e.g., broth and soup; see Boyle et al., 2016). In real life, perceptual, categorical, and symbolic generalization likely all interact to produce robust fear generalization.

A related process, known as sensory preconditioning or "behaviorally silent learning", may also explain the unexpected spread of fears. In this set of circumstances, pairings of two neutral stimuli are followed by pairings of one of these neutral stimuli with an aversive US. Subsequent presentation of the unpaired neutral stimulus may alone elicit a fear response, even though this second neutral stimulus was never directly paired with the US. For example, an individual may observe a dog at the beach (i.e., two initially neutral stimuli that have been associated together). After being bitten by a dog, being at the beach may become fear provoking, although no direct traumatic experience was associated with the beach. Sensory preconditioning thus offers one avenue for fears that emerge for no apparent reason. However, research on sensory preconditioning is scarce and its relevance for individual differences in fear and anxiety remains to be studied.

Finally, generalization may also result from poor contextualization or occasion setting of the feared stimulus. An occasion setter is a stimulus that is not directly related to the US, but moderates the response to the CS+ (Holland, 1989). For example, a tone may result in shock when in one context but not another. In this case the context "sets the occasion" for the CS-US relationship. In this case, failure to properly use contextual information to modulate responding to the CS+ would allow fear to generalize to that stimulus when presented in a variety of "safe" contexts.

3.2. Pathways by which fears may more readily generalize

Recent research investigated whether individuals with anxiety disorders or at risk for an anxiety disorder are characterized by elevated or broader levels of fear generalization. Individuals with anxiety related disorders have been found to show broader generalization of conditional fear responses to perceptually similar stimuli than healthy controls (Kaczkurkin et al., 2017; Lissek et al., 2014b, 2010). They also show a bias of greater fear generalization to generalization stimuli that are more intense than the original CS (Morey et al., 2015). One study has shown a prospective relationship between elevated perceptual generalization of fear and increased anxiety symptoms at a later date, although the onset of anxiety disorders was not measured (Lenaert et al., 2014). Despite these promising findings, some recent studies have failed to replicate elevated fear generalization in individuals with anxiety disorders compared to healthy controls (Ahrens et al., 2016; Greenberg et al., 2013; Tinoco-González et al., 2015).

High-risk designs have established a related process as a marker of risk for anxiety disorders. High trait anxious individuals were found to show delayed discrimination between a CS+ and perceptually similar safety cues in fear-potentiated startle (Haddad et al., 2012). This exaggerated perceptual generalization was, however, not found in SCRs. Other studies found elevated responding to a CS− during differential fear acquisition training (CS+ vs. CS−). Such elevated responding may represent a form of fear generalization as both CSs typically share perceptual or categorical features (e.g., both are geometric figures). In particular, not just individuals with anxiety disorders but also those high on trait anxiety show larger fear responses to the CS- than healthy controls (Duits et al., 2015; Lissek et al., 2005; Shechner et al., 2015). Elevated responding to the CS− was also observed in children at risk for anxiety disorders relative to healthy controls, which predicted child anxiety symptoms (Craske et al., 2008b; Jovanovic et al., 2014; Waters et al., 2014). Finally, elevated responding to safe stimuli correlated with neuroticism (Craske et al., 2009) and predicted subsequent anxiety disorders over a 3–4 year period (Craske et al., 2012). These high risk designs provide compelling evidence for the role of elevated fear generalization for the development and maintenance of maladaptive fear and anxiety.

A related process refers to the transfer of safety, typically assessed using AX+/AB− fear acquisition trainings followed by testing with AB relative to AX or AC (C is a novel stimulus). When the safety contained in stimulus B during initial acquisition training is "transferred" to the test phase, then responding to AB is lower than to AX or to AC, which was indeed observed in healthy controls. However, individuals with posttraumatic stress disorder show deficits in this pattern of safety transfer (see Jovanovic et al., 2012). Furthermore, such deficits predicted the persistence of self-reported PTSD symptoms (Sijbrandij et al., 2013). Thus, deficits in transfer of safety may allow fear to be expressed in more situations and to more stimuli, resulting in more fear generalization. Longitudinal studies that evaluate whether such deficits in transfer of safety are predictive of the onset of anxiety disorders are, however, lacking.

Finally, fears may generalize more readily because of deficits in the contextualization, or occasion setting, of fear learning (Waters and Craske, 2016). Individuals with anxiety disorders are less effective in using contextual stimuli to modulate their responding (Levy-Gigi et al., 2015; van Rooij et al., 2015). This deficit may allow fear to generalize beyond the contexts most associated with threat. For example, a soldier returning from combat may report fear while driving (as driving was associated with a traumatic experience), partly because she/he fails to use contextual information to determine whether driving outside of a war zone is dangerous.

Overall, there is promising evidence suggesting differences in fear generalization between individuals with anxiety disorders and healthy controls, but some studies failing to show differences between anxious and healthy individuals require further explanation. A detailed understanding of the underlying processes may help to resolve mixed findings and improve prevention and treatment of anxiety disorders. For example, fear generalization in healthy individuals seems to not only depend on learning experience, but also on instruction (Ahmed and Lovibond, 2015; Vervliet et al., 2010) or individuals rules of generalization (Wong and Lovibond, 2017). It is unclear how these factors may differ between anxious and non-anxious individuals.

In addition, understanding the neural mechanisms may provide additional insights. The neurobiology of fear generalization to stimuli that visually resemble the original CS has been linked to a variety of brain regions including the medial prefrontal cortex (mPFC), insula, nucleus reuniens and the hippocampus (Dunsmoor et al., 2011; Xu and Südhof, 2013). In regard to the hippocampus, evidence suggests a specific role for areas associated with pattern separation (dentate gyrus/CA-3), or the ability to discriminate and separate incoming neuronal information from previously stored memory traces (Besnard and Sahay, 2016). Indeed, recent evidence suggests that deficits in pattern separation are related to enhanced fear generalization (Lange et al., 2017). Individuals with anxiety disorders demonstrate reduced hippocampal activity during fear generalization and discrimination (Lissek et al., 2014a). Inasmuch as the hippocampus is implicated in discrimination and occasion setting, deficits in hippocampal functioning may partially explain enhanced fear generalization. In addition, genetic variations in BDNF have been related to fear generalization (Mühlberger et al., 2014). BNDF is essential for neurogenesis and synaptic plasticity in the hippocampus, and low levels may act as a genetic substrate of impoverished hippocampal functioning and heightened fear generalization. Carriers of the catechol-O-methyltransferase (COMT) Val Met polymorphism also demonstrate heightened fear to a learned safety cue and increased risk for the development of posttraumatic stress disorder (Kolassa et al., 2010). However, additional research using high-resolution fMRI of the hippocampus in anxious and at-risk populations during fear generalization, as well studies examining the interaction between genetic variants and fear generalization among anxious and at-risk subjects, is needed to more firmly establish the neurobiological substrates related to enhanced fear generalization in anxiety disorders.

3.3. Sex differences

Research on sex differences in fear generalization has primarily focused on the effect of hormones such as estrogen. In several rodent studies, males and ovariectomized females distinguished between a threatening (previously paired with shock) and neutral context, whereas non-ovariectomized females and those treated with estradiol demonstrated greater fear generalization (Lynch et al., 2013). However, in male rats, estrodial and testosterone *mitigate* fear generalization (Lynch et al., 2016). Increased fear generalization in female rats may result from the effect of estrogen on genomic processes involved in memory retrieval (Lynch et al., 2016, 2014) or impoverished safety signal learning (Day et al., 2016). Other hormones, such as cortisol, may interact with biological sex to influence fear generalization. Exogenous cortisol administration disrupted the contextualization of fear in women (SCRs and fear potentiated startle), while enhancing it in men (only fear potentiated startle) (van Ast et al., 2012). However, other studies have found the opposite, with exogenous cortisol impairing fear discrimination in men but not women (Stark et al., 2006; for a review see Merz and Wolf, 2017). Future research is needed to more precisely elucidate potential sex differences in fear generalization in humans.

3.4. Developmental issues

There is some evidence that children and adolescents show greater fear generalization than adults. In rodent studies, after pairing a CS with a US in one context, 'adolescent' rats show deficits in inhibiting fear to a novel stimulus and to the original CS in novel contexts (Hefner and Holmes, 2007; Ito et al., 2009). In human samples, adolescents (8–13 years) have shown greater generalization of fear (eye-blink startle response) from a CS to other perceptually similar stimuli than children (Glenn et al., 2012). Another study reported that children (8–10 years) showed elevated fear generalization (SCR) than adults (18 years and over; Schiele et al., 2016). Again, these findings may hint at vulnerable age periods and a non-linear relationship between age and susceptibility to fear generalization, although future research is needed.

3.5. Effect of depression

There is a dearth of research on the impact of depression on generalization processes. At least one study has demonstrated that heightened fear generalization is specific to PTSD, with depression neither increasing generalization in anxious individuals nor predicting generalization on its own (Jovanovic et al., 2010). However, given deficits in hippocampal functioning in depressed individuals (Sahay and Hen, 2007), and the importance of the hippocampus to fear generalization, discrimination, and occasion setting, accurately elucidating the moderating effect of depression on fear generalization is an important area of future research.

3.6. Paradigms

There are numerous well-validated paradigms for assessing aspects of fear generalization (Jovanovic et al., 2012; Lissek et al., 2010). However, there is a need for nuanced paradigms that examine multiple potential mechanisms of generalization. By definition, generalization stimuli (GS) relate to the original fear stimulus in several ways (perceptual, categorical) but also contain various neutral or even "safe" features. The resulting generalization of fear may result from a variety of factors including failure in perceptual discrimination, increased "weight" assigned to excitatory elements at the expense of neutral or inhibitory elements, deficits in transfer of inhibition, or failure to use contextual information to modulate responding (Struyf et al., 2015). Paradigms that assess multiple potential generalization and discrimination process simultaneously, along with neuroimaging and eye tracking, will be helpful in elucidating which processes, or combination of factors, are most responsible for increased fear generalization in anxious individuals. In addition, it will be important to employ more complex stimuli in fear generalization research. In many fear generalization paradigms, stimuli are often simple geometric shapes (e.g., Jovanovic et al., 2012; Lissek et al., 2010). However, conditional stimuli in anxiety disorders are complex and multimodal. The use of complex stimuli, across multiple sensory modalities, will provide a more ecologically valid examination of fear learning processes in anxious and at-risk individuals.

3.7. Summary: Fear generalization

In many ways, enhanced fear generalization is an essential feature of anxiety disorders. There is promising evidence that individuals with anxiety disorders demonstrate greater fear generalization than healthy controls (Lissek et al., 2014b, 2010), and increasing evidence that these deficits are related to key neurobiological differences (Lissek et al., 2014a). Despite the strength of this evidence, contradictory findings need to be understood (Ahrens et al., 2016; Greenberg et al., 2013; Tinoco-González et al., 2015). There is a need for greater precision regarding the mechanisms of enhanced generalization. So far, it remains unclear which specific processes explain fear generalization in anxious individuals, their genetic and neurobiological substrates, and how hormonal factors may differentially impact each of these processes. Finally, there is a need for more longitudinal research in at-risk individuals in order to determine the explanatory power of fear generalization in the emergence of anxiety disorders.

4. Fear persistence I – Fear extinction (deficits)

In addition to fear acquisition and generalization, aversive Pavlovian learning processes may also help to explain the persistence of fear despite experiencing the feared stimulus in the absence of the aversive outcome. These individual deficits in fear extinction learning may help to account for the persistence of fear in anxious individuals.

4.1. Mechanisms of fear extinction

Fear extinction learning refers to the reduction of conditional fear responding as a result of repeated CS presentations in the absence of the US. Following laboratory acquisition training, in which a former neutral stimulus is repeatedly paired with an aversive US, the same stimulus is presented in the absence of the US during extinction training. Such fear extinction training represents the laboratory analogue of learning during exposure-based interventions, although comprehensive exposure treatments also include various other components (such motivating approach behavior; see Pittig et al., 2018; Scheveneels et al., 2016). Importantly, recent studies provided evidence that individual differences in fear extinction learning may predict responses to exposure-based treatments (Ball et al., 2017; Forcadell et al., 2017; Waters and Pine, 2016).

Error-correction and inhibitory learning are central to extinction learning (Bouton, 1993; Miller et al., 1988; Wagner, 1981), but additional mechanisms, such as a decrement in generalization, may be at play as well (Bouton, 2004; Myers and Davis, 2007). Within a associative learning approach, inhibitory learning models assume that the original CS-US association learned during fear acquisition is not erased during extinction, but rather left intact and a new, secondary inhibitory learning about the CS-US develops (e.g., Bouton, 1993; Bouton and King, 1983). In this regard, extinction, like all forms of new learning, also involves the initial acquisition, consolidation, generalization, and later retrieval of the CS-noUS relationship. Significant advances in the neural processes underlying fear extinction support the inhibitory model of extinction learning. Whereas the amygdala is particularly active during fear acquisition (Shin and Liberzon, 2010), it appears to be inhibited by activity of the ventral medial prefrontal cortex (vmPFC)

during retrieval of extinction learning (Greco and Liberzon, 2016). Specifically, when fear extinction is tested in the context in which it occurred, it is posited that the hippocampus activates the vmPFC region which activates inhibitory interneurons in basolateral amygdala, that in turn inhibit output neurons in central amygdala to limit conditional responding (Duvarci and Pare, 2014; Milad et al., 2014). When fear extinction occurs in a different context, the hippocampus, however, may not activate the vmPFC during extinction recall such that the fear response is less inhibited.

4.2. Pathways by which fear extinction may be attenuated

Anxious individuals show several deficits in fear extinction, including the acquisition of extinction learning as well as long term extinction retention (Blechert et al., 2007; Craske et al., 2008b; Duits et al., 2015; Lissek et al., 2005; McGuire et al., 2016; McLaughlin et al., 2015b; Milad et al., 2013; Norrholm et al., 2011). Furthermore, they show deficits in vmPFC activation at extinction retest (McLaughlin et al., 2015b; Milad et al., 2013). These deficits in fear extinction in anxious individuals may relate to non-response and relapse after exposure therapy. Understanding the contribution of individual differences and underlying processes of these deficits may thus shed light on ways to optimize exposure treatments.

Since fear extinction requires the formation of a new memory trace (CS-noUS), genes involved in synaptic plasticity and long-term memory formation have been implicated in extinction in animals and humans. For example, BDNF met allele carries demonstrate impoverished extinction in both animal and human samples and BDNF is associated with decreased vmPFC activity during extinction training (Soliman et al., 2010). While BDNF Val66Met polymorphism predicted poorer response to exposure therapy in some studies (Felmingham et al., 2013), others have found no association (Santacana et al., 2016). Polymorphisms in catechol-O-methyltransferase (COMT) are also associated with deficits in fear extinction (Lonsdorf et al., 2009) and poorer response to exposure-based treatments (Lonsdorf et al., 2010). COMT is related to dopaminergic functioning, and dopamine has been related to error-correction processes (Abraham et al., 2014). Thus, impaired dopamine signaling may impact fear extinction and exposure response. However, there is need for research with larger sample sizes to fully elucidate the genetic and epigenetic factors that contribute to impoverished fear extinction and response to exposure therapy.

Another individual factor that may affect fear extinction is early life adversity. Animal models have shown that early life stress and adversity increase resistance to fear extinction (Cowan et al., 2013; Long and Fanselow, 2012; Remmes et al., 2016). More specifically, early life adversity has been linked to deficits in safety learning (i.e., learning that CSs do not or rarely predict a US; Wright et al., 2015) and corresponding alterations in the prefrontal cortex, amygdala, and hippocampus (Maren and Holmes, 2016). In human samples, childhood maltreatment may similarly result in structural and functional alterations in neural areas associated with threat detection, emotion regulation, or reward anticipation (Teicher et al., 2016; Teicher and Samson, 2016). These alterations include reduced prefrontal–hippocampal and reduced prefrontal–amygdala connectivity (Herringa et al., 2013). Given these findings on the association between early life adversity and deficits in safety learning as well as neural alterations related to fear extinction (Kundakovic et al., 2015; Maren and Holmes, 2016; Roth et al., 2009; Wright et al., 2015), it is plausible that early life adversity impairs later fear extinction in humans. Two recent studies in children and adolescents (McLaughlin et al., 2015a) and young adults (Scharfenort et al., 2016), however, did not find differences in fear extinction between individuals with and without a history of maltreatment. However, such data in human samples are limited. Further research in humans is needed to pinpoint the relationship between specific forms of maltreatment in childhood and adolescence and impaired fear extinction in adulthood (see Teicher and Samson, 2016).

4.3. Pathways by which fear extinction may be enhanced

Recognition of deficits in fear extinction has stimulated a body of research on potential enhancement strategies to boost extinction learning. For example, advances have been made by using neuromodulation (see Marin et al., 2014; Peña et al., 2014; Rodriguez-Romaguera et al., 2015) or biological agents to enhance fear extinction such as d-cycloserine (DCS). DCS is an antibiotic, glutamatergic agent, and partial agonist at the glycine recognition site of the N-methyl-D-aspartate (NMDA) receptor in the amygdala. As new emotional learning is mediated via NMDA receptor activation (Davis, 2011), DCS should enhance associative learning. Indeed, studies with animal models strongly suggest that DCS facilitates the process of extinction of conditioned fear (Walker et al., 2002). However, meta-analyses of human studies yielded mixed results. For example, Rodrigues et al. (2014) concluded that DCS augments exposure but with a relatively small effect size ($d = -0.34$; 95% CI: -0.54, -0.14). Another meta-analysis (Ori et al., 2015) concluded that DCS did not augment exposure relative to placebo for either children/adolescents or adults with anxiety disorders. Conceivably, the effect sizes are much smaller in human than animal studies due to negative interactions with antidepressants in human samples; antidepressants affect functioning of the glycine/NMDA receptor. In support of this notion chronic use of imipramine negated any benefit of DCS in an animal model (Werner-Seidler and Richardson, 2007), and antidepressant use in combination with DCS resulted in inferior outcomes following exposure therapy for obsessive-compulsive disorder (Andersson et al., 2015). However, a meta-analysis across various anxiety and trauma related disorders found no moderating effect of antidepressant use on DCS efficacy, although effect sizes for DCS were once again small (Mataix-Cols et al., 2017). It has also been suggested that DCS strengthens the fear association (rather than extinction of fear) should fear fail to reduce during exposure therapy. That is, the memory facilitating effects of DCS may paradoxically strengthen an existing fear association if there is little to no extinction learning on a given exposure trial. Consequently, overall effects may be attenuated by including individuals who do not demonstrate successful fear reduction during exposure therapy (Hofmann, 2014). However, fear reduction per se is not synonymous with learning CS-noUS inhibitory associations (see Craske et al., 2008a; Vervliet, 2013). Thus, DCS could enhance consolidation of CS-noUS associations even in the presence of sustained fear. More research is needed to identify specific populations for whom and boundary conditions for which DCS augmentation of exposure therapy may be indicated.

In addition to neuro-modulatory and pharmacological strategies, a variety of behavioral strategies have been suggested to boost fear extinction (see Craske et al., 2014; Pittig et al., 2016, 2015b). While procedural strategies target the procedure of extinction training itself, flanking strategies aim at providing optimal pre- and post-processing of extinction training (Pittig et al., 2016). Procedural strategies mostly focus on maximizing the mismatch between fear-related expectancies and actual experience to boost new learning as well as reduce the context-specificity of extinction learning (e.g., Craske et al., 2014, 2008a; Culver et al., 2018; Pittig et al., 2016, 2015b). Flanking strategies are based on the fact that extinction learning represents new learning and requires memory consolidation and recall. To this end, flanking strategies target processes that increase learning in general such as memory consolidation (e.g., sleep after extinction training; Kleim et al., 2014), or memory retrieval (e.g., use of retrieval cues or rehearsal strategies; Culver et al., 2011; Mystkowski et al., 2006). Most of these strategies have only been applied in experimental settings or with clinical analog samples and little is known about the utility in naturalistic exposure therapy. In addition, little is known about individual differences in responding to these strategies. Thus, an essential agenda for future research is to pinpoint which strategies work for whom to optimize extinction learning during exposure for individual patients.

A different strategy aims to target the original fear acquisition memory by making use of the reconsolidation process following the retrieval of an already consolidated memory. In general, the consolidation window is limited and once consolidated, memory is less susceptible to interference. Recent research has demonstrated that, under certain conditions, retrieval of the memory via presentation of the CS+ can render the mnemonic trace susceptible to modification. Once a memory becomes labile, it requires molecular processes such as protein synthesis in order to "reconsolidate". Targeted behavioral or pharmacological agents that disrupt this reconsolidation process may therefore prove useful as an intervention strategy aimed at "erasing" the original excitatory association (Nader et al., 2000; Schiller et al., 2010; Soeter and Kindt, 2015a, 2015b). However, there are numerous boundary conditions on inducing memory lability that may hamper its translational utility. For example, evidence suggests that when the reminder stimulus or context differs from original learning, which is almost inevitable in exposure therapy, reconsolidation may not be induced but rather a new memory trace is formed (Besnard, 2012; Bozon et al., 2003; Debiec et al., 2006; Hupbach et al., 2009; Osan et al., 2011; but see Duvarci and Nader, 2004; Nader et al., 2000). This is consistent with an evolutionary account of memory updating, as it would not be advantageous to update biologically significant associations of threat unless the exact stimulus and contexts were once again present (Treanor et al., 2017). In addition, the optimal duration of the reminder trial necessary to induce reconsolidation is unclear, and may depend critically on the relation between the reminder trial and duration of the CS during initial fear acquisition (Alfei et al., 2015). Of course, this presents obstacles to clinical translation as it is often unclear, or impossible, to determine the length of the CS during initial fear acquisition. Disrupting reconsolidation also targets the emotional component of memory, leaving the declarative CS-US memory intact, and could therefore still drive avoidant behavior and maintain pathology (Treanor et al., 2017). Reconsolidation appears to represent a fundamental capacity of memory under certain conditions, but additional detailed empirical work is needed to further explore its clinical utility (for a review see Treanor et al., 2017).

4.4. Pathways by which fear extinction may fail to generalize

In traditional laboratory fear extinction models of exposure therapy, fear is acquired to a distinct stimulus and the exact same stimulus is subsequently presented in the absence of the US. It is highly unlikely that a clinician will have access to the *original* CS during treatment: exposure therapy is usually conducted with generalization stimuli (GS) that are perceptually, categorically, or semantically related to the original CS. However, several experimental studies have demonstrated impaired generalization of fear extinction when extinction is conducted with a GS as opposed to the original CS (Barry et al., 2016; Vervliet et al., 2004; Vervliet and Geens, 2014). In terms of mechanisms, although fear extinction will proceed normally to features of the GS that are in common with the CS, any features that are absent will retain their excitatory association. Thus, when the individual confronts either the original CS or a stimulus that contains un-extinguished features, fear may return. For example, therapy for a sexual assault survivor may entail exposure to stimuli that resemble the original perpetrator (e.g., men of certain age). However, additional features (e.g., a certain smell or cologne) may not be present during the exposure and may contribute to a return of fear at a later date.

In addition, the presence of novel elements alongside excitatory features during fear extinction may lead to less overall fear extinction learning and a greater risk of fear renewal. A generalization stimulus is, by definition, a stimulus that contains excitatory elements (features in common with the CS+) as well as unique or novel elements. During fear extinction, decreases in associative strength will reduce the excitatory strength of the elements shared with the original CS+. However, the novel or unique elements may contain no inherent associative strength, and therefore decreases in associative strength during fear extinction will gradually transform these novel elements into conditional inhibitors. As inhibition accrues to these novel elements, they will gradually reduce, or protect, the excitatory elements from extinction (Rescorla, 1969; Vervliet and Geens, 2014). Consequently, fear extinction to those elements will be impaired.

For these reasons, exposure therapy with generalization stimuli will be weakened. However, additional factors may mitigate the detrimental effects of generalization stimuli during exposure therapy. For example, most individuals seek treatment many years after they acquired their fear. Experimental research suggests that the greater then length of time since fear acquisition, the greater the amount of "forgetting" of stimulus features, resulting in attenuation of the distinction between the original CS and generalization stimuli (Riccio et al., 1984; Thomas and Lopez, 1962; Wiltgen and Silva, 2007), although this attenuation has been shown to be relatively modest (Bouton et al., 1999). In addition, if individuals with anxiety disorders show deficits in hippocampally dependent discrimination processes (as discussed previously), then they may generalize more between the original CS and a GS used in exposure. To date, there has been no research examining generalization of extinction across stimuli in anxious individuals. Should research continue to substantiate the negative impact of generalization stimuli on fear extinction generalization in anxious individuals, exposure therapy could be supplemented with behavioral or pharmacological strategies to enhance the generalization of fear extinction. The exact mechanisms involved in the generalization of fear extinction and their relevance to anxiety disorders represent a major future challenge.

4.5. Sex differences

Earlier studies indicated slower fear extinction among females than males (Guimarães et al., 1991; Johnsen, 1993). A failure to replicate by Fredrikson et al. (1976) was attributed by Hedlund and Chambless (1990) to their use of variable levels of aversive stimuli, where one is less likely to see sex differences in fear extinction perhaps because females choose a weaker US. In contrast, Guimarães et al. (1991) used a standardized 100 DB white noise for all participants. More recently, evidence has highlighted variations by hormonal status, with low levels of estrogen associated with impaired fear extinction (Glover et al., 2015, 2012; Hwang et al., 2015; Lebron-Milad et al., 2012; Merz et al., 2012b). Zeidan et al. (2011) found that high estradiol is associated with increased vmPFC activation during fear extinction recall as well as less SCRS than those low in estradiol. In addition, reduced prefrontal–amygdala connectivity following early life adversity has only been found in females (Herringa et al., 2013). These findings may suggest that females are less likely to extinguish their fears naturalistically or to fare well with exposure therapy during the follicular or ovulatory phases of their menstrual cycle. Again, further research is needed to fully explore the role of sex in fear extinction differences and their relation to anxiety disorders.

4.6. Developmental issues

There is evidence to suggest that fear extinction is impaired in adolescents relative to adults. For example, adolescents show elevated SCR to the CS+ across extinction training relative to children and adults (Pattwell et al., 2012). Data presented by Britton et al. (2013) suggest that fear-potentiated eye-blink startle to a CS+ relative to a CS− during extinction training was greater in adolescents than adults, although group differences disappeared by the last trial. These findings are in line with rodent research suggesting that adolescence, but not infancy, is linked to impaired fear extinction (see Maren and Holmes, 2016; Pattwell et al., 2012). Studies that have failed to replicate impaired extinction grouped younger children and adolescents into the same group (e.g., Jovanovic et al., 2014; Shechner et al., 2015).

The impairment in fear extinction observed in adolescents has been

attributed to slower maturation of prefrontal cortical areas implicated in extinction learning (e.g., vmPFC; Johnson and Casey, 2015). Rodent studies have elucidated neural mechanisms such that during infancy, down-regulation of fear is controlled via the amygdala, through signaling from the basolateral amygdala (BLA) to the central amygdala (CeA; Kim and Richardson, 2010). The vmPFC that has been implicated in extinction learning matures across adolescence into adulthood and eventually assumes a more central role in regulating the amygdala (Kim and Richardson, 2010). Consequently during adolescence, while the medial PFC is maturing, it plays a limited role in inhibition of the amygdala's response to fear-relevant stimuli (Dreyfuss et al., 2014; Hare et al., 2008). In support, activity between these two regions is more strongly negatively coupled in the mature, adult brain than in adolescence (Gee et al., 2013). These findings open an exciting area of research that may explain the onsets of anxiety disorders during adolescence.

4.7. Effect of depression

There has been almost no investigation of the impact of depressive symptoms, or depressive disorder diagnoses, on fear extinction. One study reported enhanced fear extinction in individuals with unipolar depression without comorbid anxiety disorder compared to healthy controls (Kuhn et al., 2014). Further research is needed to replicate this finding and examine any potential impact of depressive symptoms on fear extinction in anxious samples.

4.8. Paradigms

Research examining generalization of fear extinction typically examines generalization of extinction across time (i.e., extinction retention) and contexts. However, successful fear extinction would also require the ability to generalize extinction learning across stimuli. Unfortunately, there is a dearth of research in this area. There is need for translational research to employ more externally valid fear extinction paradigms, including generalization stimuli during extinction and the use of complex CSs that incorporate more than visual cues (e.g., auditory, olfactory), to further elucidate a) differences between anxious individuals and healthy controls in generalization of fear extinction following extinction with a GS, b) how fear extinction with a GS and subsequent extinction generalization may predict response to treatment, and c) whether these processes mediate treatment response.

4.9. Summary: Extinction learning

There is well-documented support that evidence-based treatments for anxiety disorders operate via associative learning processes. Indeed, aversive Pavlovian learning and its neural substrates change as a result of exposure therapy and these changes co-vary with symptom improvement (Helpman et al., 2016; Kircher et al., 2013; Lueken et al., 2013). Moreover, individual differences in aversive Pavlovian learning predict responses to exposure-based treatments (Ball et al., 2017; Forcadell et al., 2017; Waters and Pine, 2016). Similarly, genetic polymorphisms related to extinction learning predict response to exposure therapy (e.g., Felmingham et al., 2013; Fullana et al., 2012). Strikingly, individuals with anxiety disorders demonstrate deficits in fear extinction, which may partially explain the persistence of fear following naturalistic or structured exposure. Developmental factors, particularly those associated with adolescence, and hormonal processes may contribute to impairments in fear extinction. Key evidence is accumulating regarding the neurobiological and genetic substrates of these extinction learning deficits, although there is a need for additional research employing more complex paradigms and stimuli to further elucidate the precise nature of extinction learning deficits in anxious samples. Finally, there is a strong need for large-scale clinical trials examining the impact of behavioral strategies targeting fear extinction processes on the success of exposure therapy.

5. Fear persistence II – Avoidance behavior

Besides deficits in fear extinction, avoidance behavior is a major mechanism presumed to contribute to the persistence of fear and anxiety. Avoidance responses are triggered when actual or perceived threat activates the defensive motivational network to improve survival chances through ensuring protection (Dickinson and Dearing, 1979; Lang, 1995). Avoidance and escape behavior may be broadly defined as any external or internal response that increases the physical or psychological distance between an organism and an actual or perceived threat or aversive event. More specifically, avoidance can be distinguished from escape with avoidance resulting in the omission of an upcoming aversive event and escape resulting in the termination of an already ongoing aversive event. Furthermore, active and passive forms of avoidance are separated by whether an active behavioral response *(active avoidance)* or an inhibition of a response *(passive avoidance)* is required to prevent the aversive event.

5.1. Mechanisms of avoidance

Avoidance learning was traditionally conceptualized as instrumental learning process. In instrumental learning, responses to a stimulus are reinforced or weakened by their positive or negative outcomes. In the classical two-factor theory (Miller, 1948; Mowrer, 1960, 1951; Mowrer and Lamoreaux, 1946), avoidance is assumed to be negatively reinforced as the aversive state of fear is reduced after an avoidance response is performed. Importantly, there is also a Pavlovian component to avoidance learning (Krypotos et al., 2014; LeDoux et al., 2017; Rescorla and Soloman, 1967). Recently, it has been suggested that avoidance learning involves different sequential learning processes (LeDoux et al., 2017). Aversive Pavlovian learning, as the initial process, results in defensive reactions such as attentive freezing or reflexive startle responses. More flexible avoidance responses are subsequently learned in relation to their outcomes, i.e., are shaped by instrumental processes. Finally, these responses may turn into avoidance habits due to overtraining that do not depend on outcomes anymore (LeDoux et al., 2017; Ruge and Wolfensteller, 2010). Thus, avoidance forms an essential aspect of associative learning processes involved in the development and maintenance of anxiety disorders.

Other theoretical approaches have highlighted the distinction between reflexive and reflective processes in the learning and expression of avoidance (see Arnaudova et al., 2017; Krypotos et al., 2015). Reflexive processes and responses are rapid, automatic, and linked to automatic stimulus-response associations. In contrast, reflective processes and responses are slow, elaborate, controlled, and regulated by expected outcomes and current goals (e.g., Strack and Deutsch, 2014). The predominance of each of these systems for defensive behavior seems to depend on the proximity of threat. In animals, different threat proximities are associated with distinct states of the defense cascade (Fanselow and Lester, 1988). In line with this threat proximity continuum, human defensive behavior may be more strongly guided by reflexive processes under proximal threat or by higher-order reflective processes under distal threat, with each process associated with distinct underlying neural mechanisms and physiological responses (Löw et al., 2015; Mobbs et al., 2010, 2009, 2007; Wendt et al., 2017). Integrating the concept of reflexive and reflective responses with the sequential learning processes of avoidance, we suggest that defensive reactions as result of Pavlovian learning and habitual responses as result of habit learning represent rather reflexive responses that are guided by preceding stimuli. Avoidance responses shaped by instrumental learning processes comprise a stronger reflective component. Given these different learning and response pathways, their distinct contribution to maladaptive avoidance in anxiety disorders needs to be addressed.

5.2. Pathways of elevated avoidance

Avoidance learning may involve different processes for defensive reactions, instrumental avoidance, and avoidance habits. Importantly, there is first evidence for distinct imbalances in these processes in anxious individuals.

5.2.1. Defensive reactions

Defensive reactions in aversive Pavlovian learning are, for example, investigated using the fear-potentiated startle response (Lonsdorf et al., 2017). As part of the defensive network output, the startle response is potentiated by negative stimuli such as unpleasant or fear-relevant images (Hamm et al., 1997, 1993; Lang et al., 1998). The potentiation of the startle response serves a preparatory function to rapidly engage in fight-flight behaviors and can especially be observed during approaching, uncontrollable threat (Löw et al., 2015; Wendt et al., 2017). Numerous studies indicate that fear acquisition training potentiates the startle response to a CS+ in healthy and anxious individuals (e.g., Davis et al., 1993; Duits et al., 2015; Grillon and Morgan, 1999; Hamm et al., 1993). Meta-analyses and reviews conclude that there are either no differences in such fear-potentiated startle responses between anxious and healthy individuals or present mixed results (Duits et al., 2015; Grillon, 2002; Lissek et al., 2005). In contrast, a series of studies showed elevated baseline startle responses but no differences in stimulus-dependent startle responses in individuals with anxiety disorders compared to healthy individuals (Grillon, 2002). These data suggest that anxious individuals do not show elevated defensive reactions to distinct stimuli that signal obvious and imminent threat (i.e., strong situations; Lissek et al., 2006), but to contextual stimuli that signal potential, not imminent threat (e.g., Grillon and Morgan, 1999).

Other measures of reflexive responses are automatic action tendencies. Automatic avoidance tendencies are, for example, assessed as fast avoidance-related motor responses, such as quickly pushing a joystick to “push away” a stimulus. Such responses are facilitated by negative stimuli in healthy individuals (Phaf et al., 2014). Elevated avoidance tendencies have been found for fear-relevant stimuli, such as spider stimuli in spider fearful adults and children (Klein et al., 2011; Rinck and Becker, 2006), angry and happy faces in socially anxious individuals (Heuer et al., 2007), sexual images for individuals with sexual trauma (Fleurkens et al., 2014), and contamination images in individuals with contamination fears (Amir et al., 2013). These elevated avoidance tendencies might hint at elevated defensive reactions in anxious individuals when confronted with a feared stimulus. Alternatively, elevated avoidance tendencies might also be seen as a product of stronger habitual avoidance, because fear towards the specific stimuli most likely existed well before the assessment of avoidance tendencies in these studies. Supporting the former hypotheses of elevated defensive reactions, one study showed that elevated avoidance tendencies may be newly acquired for formerly neutral stimuli by means of fear acquisition training (Krypotos et al., 2014). However, no studies to date have investigated whether such acquisition of automatic avoidance tendencies is elevated in individuals with anxiety disorders or at-risk for anxiety disorders. Thus, more research on the link between fear acquisition and automatic action tendencies, its underlying mechanism, and potential individual differences is needed.

5.2.2. Instrumental avoidance

More reflective processes of avoidance are typically investigated in instrumental learning paradigms. Healthy and anxious individuals typically learn to perform arbitrary responses to prevent an upcoming US (e.g., pressing a button or selecting specific card decks; Aupperle et al., 2011; Delgado et al., 2009; Lovibond et al., 2008; Ly and Roelofs, 2009; Sierra-Mercado et al., 2015; Talmi et al., 2009). Likewise, individuals avoid virtual environments that previously predicted aversive events (e.g., Glotzbach et al., 2012; Grillon et al., 2006) as well as naturalistic fear stimuli in open field tests (Walz et al., 2016). Reflective avoidance responses typically persist in the absence of aversive consequences, which prohibits fear extinction learning and thus contributes to a loop of sustained fear and ongoing avoidance (Lovibond et al., 2009). Moreover, avoidance responses may persist after successful fear extinction and trigger a later return of previously extinguished fear (van Uijen et al., 2017; Vervliet and Indekeu, 2015). Finally, engaging in avoidance behaviors may itself be used as evidence for potential threat, even during safety, and thereby increase threat appraisal and fear (Engelhard et al., 2015; Van Den Hout et al., 2014; van Uijen et al., 2017; van Uijen and Toffolo, 2015; Vervliet and Indekeu, 2015).

There is some evidence that instrumental avoidance learning is elevated in anxious individuals. Anxious children show elevated instrumental avoidance to angry faces compared to non-anxious children (Lau et al., 2012; Lau and Viding, 2007). Moreover, anxious adolescents are more likely to refuse (i.e., avoid) participation in studies involving aversive USs than their non-anxious counterparts (Britton et al., 2013; Waters et al., 2009). Simple instrumental learning tasks have yielded mixed findings in anxious adults, with some evidence for faster avoidance acquisition in response to fear-relevant stimuli (Dymond et al., 2014), but also to safe stimuli (CS-; Vervliet and Indekeu, 2015), or a complete lack of differences compared to healthy individuals (Ly and Roelofs, 2009). However, ceiling effects in these simple tasks may preclude differential performance (i.e., strong situation effect).

Pronounced avoidance has more consistently been reported in *Behavioral Approach Tests* (BATs). In a typical BAT, individuals are asked to approach a fear-relevant stimulus step-by-step (e.g., moving closer to a spider; Zoellner et al., 2000) or endure in a fear-relevant situation (e.g., remaining in a confined space; Valentiner et al., 1996). These tests thus require reflective control over the tendency to avoid such situations. Anxious individuals typically show less or slower approach or terminate the test more quickly (e.g., Olatunji et al., 2008; Rinck et al., 2010; Tolin et al., 1999; Vorstenbosch et al., 2012; Williams et al., 1989). Similar findings were found in virtual environments for socially anxious or spider fearful individuals (Rinck et al., 2016, 2010). However, avoidance in BATs can be strongly biased by specific instructions and are susceptible to demand effects (Bernstein and Nietzel, 1974, 1973; Trudel, 1979). In addition, BATs mostly offer a simplified choice between approaching vs. avoiding a single feared stimulus, neglecting the complexity of multiple outcome situations in real life. Thus, there is a need for more sophisticated designs to fully understand the pathological mechanisms of avoidance in anxiety disorders (Beckers et al., 2013).

In this regard, mixed outcome approach-avoidance designs are useful for modelling more complex behaviors and behavioral conflicts (see Pittig et al., 2014c). In most everyday situations, different behaviors are linked to diverse positive and negative outcomes. When reward and threat are anticipated outcomes of the same action, the motivational approach and avoidance systems are in conflict with each other and a decision conflict arises (see Corr, 2013). Healthy individuals, for example, avoid negative stimuli when competing rewards are lacking, too small, or uncertain, but will approach the same negative stimuli when sufficiently rewarded (Aupperle et al., 2011; Pittig et al., 2014c; Rattel et al., 2017; Sierra-Mercado et al., 2015). Conversely, healthy individuals avoid more profitable decisions when these decisions are linked to presentations of a CS+, which was previously paired with an aversive US (Pittig et al., 2014c). Importantly, such costly avoidance is elevated in highly trait anxious individuals (Pittig et al., 2014c) as well as spider fearful individuals and socially anxious individuals (Pittig et al., 2014a, 2014b). It is also susceptible to other fear acquisition pathways as it is also triggered by instructed threat stimuli (Bublatzky et al., 2017) or generalization stimuli (Hunt et al., 2017; van Meurs et al., 2014). As these avoidance responses are related to costs, conflict paradigms may help to account for the impairments associated with pathological avoidance in anxiety disorders. In this regard, costly avoidance has been linked to worse treatment outcome in patients with social anxiety disorder (Pittig et al., 2015a).

Combined, these findings suggest that anxious individuals possess less reflective control of avoidance in complex mixed-outcome decisions. On the other hand, elevated costs of avoidance or incentives for approaching a fear-relevant stimulus may reduce avoidance behaviors (Aupperle et al., 2011; Bublatzky et al., 2017; Rattel et al., 2017; Sierra-Mercado et al., 2015) and thereby represent an important asset to initiate exposure exercises. For example, the first exposure to air travel may be increased by highlighting benefits of this behavior such as being able to go on desired vacations or visits of friends and family. Future studies are, however, needed to pinpoint the underlying mechanisms of the development and change in complex reflective avoidance. To date, there is little research investigating potential individual differences modulating elevated avoidance responses.

5.2.3. Habitual avoidance

Whereas behavioral responding in novel situations is initially more instrumental and guided by actual outcomes, it may quickly turn into a habitual response due to overtraining (Ruge and Wolfensteller, 2010). Such behavioral habits are again more reflexive as they are driven by preceding stimuli and overlearned stimulus-response associations (Dezfouli and Balleine, 2012). Instrumental avoidance may thus become a habitual response that is less sensitive to the actual outcomes (see also LeDoux et al., 2017). For example, whereas washing hands after contact with sanitary objects may initially be instrumental to minimize perceived threat of contamination, the mere sight of such objects may later suffice to trigger habitual washing. Indeed, some evidence suggests that acquisition of avoidance habits is elevated in individuals with OCD. After repeatedly responding to avoid an aversive US, individuals with OCD kept executing the same response although they knew that the US could not occur anymore (as electrodes were disconnected; Gillan et al., 2014). Interestingly, this elevated habitual avoidance compared to healthy controls was found in the absence of group differences in fear learning. In a follow-up fMRI study, enhanced avoidance habits were associated with elevated activity in the nucleus caudate, a brain region linked to goal-directed response-outcome learning (Gillan et al., 2015). Thus, deficits in goal-directed control during habit-goal competition may underlie the stronger expression of avoidance habits in OCD. Strong avoidance habits may also help to explain why avoidance persists despite successful fear extinction (van Uijen et al., 2017; Vervliet and Indekeu, 2015). Summarized, learning of habitual avoidance may be more pronounced in anxious individuals, which may help to explain the persistence of anxiety disorder symptoms. However, research is still scarce and few studies have investigated avoidance habit learning in individuals with disorders other than OCD. Given the important role of habitual avoidance for the long-term aggravation of anxiety disorders, this lack of research represents a major gap for future research.

5.3. Generalization of avoidance

Similar to fear, avoidance behavior may spread through different forms of generalization. In healthy individuals, generalization to perceptually similar CSs has been shown for avoidance learned by direct experience as well by instruction or observation (Cameron et al., 2015; van Meurs et al., 2014). Moreover, avoidance behavior may spread to semantically and symbolically generalized CSs in healthy individuals (Augustson and Dougher, 1997; Boyle et al., 2016; Dymond et al., 2011). For example, avoidance of knives or scissors due to the fear of hurting ones child may generalize to other stimuli, which are idiosyncratic “deadly objects”, but perceptually not similar (e.g., tools, sports gear, etc.).

There is tentative evidence for elevated generalization of avoidance behavior in anxious individuals. Specifically, individuals high on neuroticism showed elevated avoidance in the presence of stimuli that were perceptually similar to a previously learned CS+ (Lommen et al., 2010). In another study, individuals learned to perform an avoidance response in the presence of a CS to avoid an upcoming spider pictures. In spider fearful individuals, these avoidance responses subsequently generalized more strongly to symbolically related CSs than in non-fearful individuals (Dymond et al., 2014). However, as spider fearful individuals also required more generalization training, further replications are required. Thus, future research is warranted to fully determine the extent of and individual factors contributing to elevated generalization of avoidance in maladaptive fear and anxiety.

5.4. Sex differences

Sex differences are particularly pronounced with respect to avoidance behavior. For example, the proportion of females increases as severity of agoraphobic avoidance intensifies (Cameron and Hill, 1989; Thyer et al., 1985). In BATs, fearful females have been observed to be more avoidant than fearful males (McLean and Hope, 2010; Speltz and Bernstein, 1976; Stoyanova and Hope, 2012). In addition to biological sex, the impact of gender roles has been implicated. For example, men who reported higher levels of expressivity, typically associated with femininity, showed elevated avoidance (McLean and Hope, 2010). However, this result could not be replicated (Stoyanova and Hope, 2012). As an explanation for elevated avoidance in females, it has been theorized that boys might be more encouraged to confront fears during childhood than girls (McLean and Anderson, 2009), which may result in less avoidance of feared stimuli. However, these ideas remain to be tested.

In animal studies, female rodents show facilitated acquisition of active avoidance responses (Dalla and Shors, 2009). These findings have been translated to human experimental studies. In a videogame paradigm, for example, participants had to move a spaceship to gain points during safe periods, but had to hide in safe areas to avoid losing points during threat. Threat periods were always preceded by a warning signal (CS+). After onset of the warning signal, females engaged in avoidance earlier but not more often than males (Sheynin et al., 2014a, 2014b). By applying computational reinforcement-learning models, this more rapid avoidance response was linked to an increased sensitivity to punishment in females (Sheynin et al., 2015). As the aversive stimulus in these experiments was “losing points”, the degree to which the findings translate to more aversive USs and activate fear-relevant networks in the brain is unknown (see Mineka and Öhman, 2002). However, when individuals could choose between approaching negative pictures to earn more points, females also showed more frequent avoidance compared to males (Aupperle et al., 2011). Thus, evidence suggests that avoidance is elevated in females, which may help to explain the higher prevalence of anxiety disorders. Similar to fear learning, more research is needed to investigate underlying moderators and mediators of avoidance. Unlike research in fear learning, research on the impact of menstrual cycle or hormones in avoidance learning is scarce.

5.5. Developmental issues

In rodent studies, the acquisition and especially the retention of acquired avoidance is impaired in younger, immature rodents compared to adults (Egger and Livesey, 1972; Kirby, 1963; Schulenburg et al., 1971). Few studies have investigated developmental effects on avoidance behavior in humans. Adolescents compared to children with social anxiety disorder reported more avoidance of specific social situations (Rao et al., 2007; Sumter et al., 2009). However, it is unclear to what extent such age effects may be confounded by longer durations of (sub-) clinical fear. To the best of our knowledge, there are no studies directly testing the effect of age on avoidance learning in humans within an associative learning model.

5.6. Effect of depression

Self-report of avoidance and depression are typically highly correlated (e.g., Moulds et al., 2007; Ottenbreit and Dobson, 2004). Avoidance as a function of anxiety, and the associated functional impairments, is often seen as a leading cause for secondary depression (Jacobson and Newman, 2014; Wittchen et al., 2003). It also seems reasonable that elevated depression may increase avoidance behavior, especially passive avoidance. In indirect support, women with social anxiety disorder and comorbid depression indicate higher avoidance compared to women with either disorder alone (Ottenbreit et al., 2014). Furthermore, higher self-reported depression has been shown to be mildly associated with elevated avoidance in a BAT (Davis et al., 2013). However, to the best of our knowledge, there are no studies directly testing the effect of depression on avoidance acquisition and extinction in individuals with anxiety disorders.

5.7. Paradigms

Similar to fear learning paradigms, unambiguous avoidance paradigms may not capture the complexity of human behavior and anxious psychopathology. In paradigms involving unambiguous contingencies between simple avoidance actions (pressing a button or not) and a single aversive outcome (US omitted vs. not), avoidance is highly adaptive to prevent an aversive event. Unambiguous paradigms thus result in fast and strong avoidance acquisition, limiting the investigation of individual differences that may be relevant for the development and maintenance of anxiety disorders. Again, a stronger focus on more ambiguous designs, for example avoidance generalization or lower reinforcement rates, may help to better understand the crucial mechanisms of avoidance learning for anxiety disorders. Paradigms should also aim to model the pathological quality of avoidance and account for multiple and mixed outcomes of behavior to increase the ecological validity of avoidance research. In this regard, modelling the costs of avoidance is essential (see Pittig et al., 2014a, 2014b, 2014c; Rattel et al., 2017; Vervliet and Indekeu, 2015). In anxiety disorders, pathological avoidance reduces irrational fears in the short-run, but vitally impedes the individual from attaining other positive outcomes. For example, avoiding social events may reduce the fear of embarrassment, but at the same time impede making new friends (Kashdan et al., 2008). Given this preference for short-term relief at the cost of other rewards, paradigms modelling approach-avoidance conflicts may help to provide further understanding of pathways into psychopathology.

5.8. Summary: Avoidance behavior

There is strong evidence that different learning processes involved in avoidance are imbalanced in individuals with anxiety disorders or at-risk for anxiety disorders. Such elevated avoidance prevents extinction learning and thereby maintains fear and anxiety. This may help to explain less than optimal effects of exposure-based treatments. In support, higher baseline avoidance predicts poorer treatment outcome and may also be an important moderator for outcome of different types of treatment (Davies et al., 2015; Mesri et al., 2017; Pittig et al., 2015a). Furthermore, epidemiological models highlight the crucial role of sustained avoidance for functional impairment and dysfunctional developmental pathways typically associated with anxiety disorders (Wittchen et al., 2011) and the development of secondary depression (Beesdo et al., 2007; Wittchen et al., 2003).

However, there is little known about specific mechanisms, such as avoidance generalization, avoidance extinction, the formation of avoidance habits, or individual differences in avoidance learning. Although there is converging evidence that avoidance acquisition is elevated for females, the underlying processes and contributing factors (e.g., hormones) are poorly understood. Moreover, little is known about how other individual differences pertinent to anxiety disorders such as age or symptoms of depression alter avoidance learning. More complex models, such as generalization or mixed outcome approach-avoidance paradigms, may provide more ecologically valid tests for this endeavor. Overall, research on avoidance only recently (re)emerged (e.g., Arnaudova et al., 2017; Beckers and Craske, 2017; LeDoux et al., 2017; Servatius, 2016). Given the prominent role of avoidance for anxiety disorders and their treatment, this major research gap needs to be addressed by future experimental and clinical research.

6. Return of fear

6.1. Mechanisms of fear resurgence

As described previously, inhibitory learning and regulation is thought to be a central mechanism of fear extinction. From an associative learning perspective, the new CS-noUS association is impacted by both the CS and the context in which the CS is presented, whereas the initial excitatory association is largely independent of context (Bouton, 2004). More specifically, the CS is assumed to possess two meanings after extinction; its original excitatory meaning (CS-US) as well as an additional inhibitory meaning (CS-noUS). Therefore, even though fear subsides when experiencing the CS in the absence of the US, retention of at least part of the original association can be uncovered by distinct experimental procedures (see Lonsdorf et al., 2017; Vervliet, 2013). Each of these procedures highlights a potential pathway how fear may return after successful treatment.

First, conditional fear shows spontaneous recovery (Quirk, 2002), meaning that the strength of the CR increases proportional to the length of time between fear extinction training and later test. The return of fear with the passage of time has been observed in multiple laboratory conditioning studies in humans (e.g., Culver et al., 2018, 2015; Huff et al., 2009; Norrholm et al., 2008; Schiller et al., 2008; Zbozinek et al., 2015). Clinically, this effect parallels the return of fear that may occur after completion of exposure therapy (e.g., Craske and Mystkowski, 1999; Craske and Rachman, 1987). Thus, a patient whose fear of air travel significantly reduces by the end of treatment is vulnerable to a return in fear of flying if air travel is not continued following treatment completion.

Second, renewal of conditional fear occurs if the surrounding context is changed between fear extinction training and later test (Bouton, 1993). In other words, fear extinction is somewhat specific to the context in which it occurs. This context-specificity has been observed in human fear conditioning studies (e.g., Bandarian-Balooch et al., 2012; Holmes and Westbrook, 2014; Neumann, 2006) and in clinical analog samples undergoing exposure therapy (Culver et al., 2011; Mystkowski et al., 2006, 2003, 2002). The clinical relevance of renewal arises when exposure therapy is completed in one or only a limited number of contexts (e.g., the presence of a therapist or always within therapy sessions). Fear is then likely to return when the feared stimulus is subsequently encountered in a different context (e.g., when alone or when unrelated to a therapy session).

Third, reinstatement of conditional fear occurs if unsignaled (or unpaired) US presentations occur in between extinction training and retest (Rescorla and Heth, 1975) and has been observed in laboratory conditioning studies in humans (e.g., Hermans et al., 2005; Van Damme et al., 2006; Zbozinek et al., 2015). The clinical implication of reinstatement is that adverse events following exposure therapy may lead to a return of fear of the previously feared stimulus if it is encountered in an anxiety inducing context. For example, fear of asking questions in work meetings may resurge at work after being rejected in another social situation or possibly even after an unrelated adverse event (such as physical illness).

Fourth, rapid reacquisition of the CR occurs with repeated CS-US pairings following fear extinction (Ricker and Bouton, 1996). Reacquisition has mostly been studied in human laboratory studies (Culver et al., 2018; Zbozinek and Craske, 2017b). The clinical

application is that fears that have subsided may be easily and rapidly reacquired with re-traumatization, as may occur when a socially anxious individual is ridiculed again after treatment.

These four mechanisms (spontaneous recovery, context renewal, reinstatement and reacquisition) may all play a role in the resurgence of conditional fear following completion of fear extinction or exposure therapy (Staples-Bradley et al., 2016). There is also some evidence for greater fear renewal in individuals with anxiety disorders. For example, both adults and children with anxiety disorders demonstrate poorer fear extinction retention, and therefore greater spontaneous recovery, than healthy controls (Craske et al., 2008b; Garfinkel et al., 2014; Marin et al., 2017; McLaughlin et al., 2015b; Milad et al., 2013, 2009b). There has been little examination of either contextual fear renewal or reinstatement in anxious samples, although at least one study has demonstrated enhanced context renewal, which corresponded with aberrant neurobiological activation in the hippocampus and amygdala, in PTSD (Wicking et al., 2016).

Besides the four return of fear mechanisms, fear may resurge following fear extinction given anxious individuals' use of "safety signals" or "safety behaviors" during exposure therapy. A safety signal or safety behavior is any stimulus (or behavior) that reduces the likelihood of the US. From an associative learning perspective, safety signals either function as conditional inhibitors or occasion setters. Conditional inhibitors are stimuli that directly predict the non-occurrence of the US (Rescorla, 1969). For example, benzodiazepine medication might function as a conditional inhibitor, in that it is believed to directly prevent a heart attack (i.e., US non-occurrence). In contrast, a negative occasion setter is not directly associated with the US, but modulates the CS-US relationship by signaling that the CS is less likely to lead to the US (Holland, 1989). Being near a hospital may function as a negative occasion setter as it modulates the likelihood that a rapid hear beat (CS) will lead to a deadly heart attack (US; see Treanor and Barry, 2017). Inasmuch as these stimuli decrease US expectancy during an exposure or fear extinction trial, they result in less overall decrease in associative change and "protect" the CS from extinction learning (Lovibond et al., 2009). Therefore, the CS maintains more of its excitatory charge and corresponding conditional response (e.g., fear).

In sum, there is some, albeit limited, evidence for an elevated return of fear and use of safety signals in anxious individuals, which helps to explain the persistence and resurgence of maladaptive fear and anxiety. However, studies in clinical samples are rare and prospective studies on the effect of these mechanisms on long-term outcome of exposure therapy are needed.

6.2. Sex differences

Higher levels of estradiol are associated with better retention of extinction learning (Graham and Milad, 2013; Zeidan et al., 2011; but see Pineles et al., 2016). However, this may be due to improved consolidation of fear extinction, and not enhanced extinction retrieval per se (Milad et al., 2009a). Unfortunately, there is a dearth of evidence examining sex differences in other fear renewal processes such as context renewal, reinstatement, and rapid reacquisition.

6.3. Developmental issues

In rodent studies, there is consistent evidence for more resurgence of extinguished fear in adolescents. For example, 'adolescent' rodents showed more spontaneous recovery of CR than juvenile and adult rodents (McCallum et al., 2010; Pattwell et al., 2012). Also, rodents who acquire CRs during adolescence show more spontaneous recovery when fear extinction also occurs in adolescence relative to when it occurs during adulthood (Baker and Richardson, 2015). One study has failed to replicate findings regarding the return of fear in adolescent rodents (Broadwater and Spear, 2013), although methodological differences between all previous studies and this latter study are likely to account for such discrepancies (e.g., differences in CS duration). Data from human samples is limited and mixed. Den et al. (2015) found no evidence of age-related differences in reinstatement of CR between adolescents and adults. Britton et al. (2013) failed to find elevated spontaneous recovery in adolescents compared to adults tested three weeks after extinction. However, they conducted conditioning and extinction outside of a MRI scanner, whereas the test phase was conducted within the scanner. Thus, a context change may have confounded age effects.

6.4. Effect of depression

The association between depression and return of fear has only been observed indirectly. Depression is associated with low levels of positive affect. Positive affect increases semantic processing, which can enhance encoding, rehearsal, and retrieval of new memories and help to better relate incoming information to already-known information (Clore and Huntsinger, 2007; Craik, 2002; Craik and Lockhart, 1972). Recently, it has been argued that positive affect may therefore enhance extinction and reduce spontaneous recovery, context renewal, reinstatement, and reacquisition (Zbozinek and Craske, 2017a). Indeed, the induction of positive affect reduced the reinstatement of fear (Zbozinek et al., 2015) and high trait positive affect was associated with less reacquisition of fear (Zbozinek and Craske, 2017b). Thus, depression, as a condition of low positive affect, may contribute to persistence and resurgence of conditional fear and limited response to exposure treatment. However, studies directly addressing this issue are missing.

6.5. Summary: Return of fear

Associative learning models describe numerous methods through which fear may return following successful extinction. There is strong evidence that individuals with anxiety disorders demonstrate deficits in the retention of extinction learning across time, although there is a need for additional research examining other mechanisms of fear renewal (e.g., context renewal, reinstatement) in anxious samples, as well as how individual differences in fear renewal processes predict long-term improvement and relapse following evidence-based treatments. In addition, it will be essential to utilize paradigms that can sufficiently differentiate whether enhanced fear renewal results from deficient extinction recall and generalization or impoverished initial consolidation of extinction learning.

7. Conclusion

Over the last decades, research on aversive associative learning has greatly contributed to our understanding of the development and maintenance of anxiety and related disorders. It offers parsimonious explanations for numerous means through which pathological fear and anxiety *emerge*, *spread*, *persist*, and *resurge* and thereby informs the optimization of prevention and treatment strategies.

Despite these advances, current research has only begun to target some of the major gaps and boundary conditions. Future research is needed to precisely elucidate core mechanisms underlying deficits in specific associative learning processes. Besides the acquisition and extinction of fear, fear and extinction generalization are crucially involved in the development of anxiety disorders and their treatment. Although individuals with anxiety disorders demonstrate heightened fear generalization, whether this is due to increased generalization, deficits in discrimination, or deficiencies in transfer of inhibition remain unclear (Struyf et al., 2015). Moreover, the underlying mechanisms of avoidance behavior, its generalization, extinction, and its interaction with fear learning are necessary to understand the complex symptomatology of individuals with anxiety disorders. In addition to expanding the mechanistic focus, research should aim to pinpoint important individual differences pertinent to anxiety disorders as moderators and mediators that shape the mechanisms underlying fear and

avoidance. In this regard, broad differences such as biological sex may be too general and require comprehensive analyses of further moderators.

On the methodological level, a shift towards more complex paradigms may help to elucidate individual differences. The use of multimodal, complex stimuli will provide more externally valid laboratory analogues, as will examination of generalization stimuli during fear extinction and subsequent generalization of extinction learning. Paradigms involving ambiguity and conflict may be useful additions to enhance the ecological validity of experimental models. This research agenda ultimately aims to inform innovative strategies to minimize avoidance and maximize fear extinction during exposure therapy. While basic research provided first controlled laboratory insights into such enhancement strategies, a further crucial gap represents the replication and test of the clinical utility in controlled and naturalistic clinical studies. In terms of treatment, there is a need for additional research examining pre- to post-treatment changes in aversive associative learning processes across a variety of anxiety disorders. Including measures of aversive associative learning throughout treatment, to assess mediation, will also be informative. Finally, additional randomized clinical trials that directly manipulate strategies to optimize fear extinction will provide additional evidence for the degree to which aversive associative learning processes act as potent mechanisms of successful treatment.

Conflicts of interest

All authors declare that they have no conflicts of interest.

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