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Avoidance of learnt fear: Models, potential mechanisms, and future directions

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ABSTRACT

Avoiding stimuli that were previously associated with threat is essential for adaptive functioning, but excessive avoidance that persists in the absence of threat can turn dysfunctional and results in severe impairments. Fear and avoidance conditioning models have substantially contributed to the understanding of safety behaviors towards learnt fear stimuli. Safety behaviors are executed in the presence of a feared stimulus to prevent the upcoming threat and are well-established in laboratory models. Avoidance of learnt fear, i.e., avoidance of the feared stimulus itself, is typically initiated before the onset of a feared stimulus: individuals oftentimes avoid fear stimuli to prevent negative emotions evoked by them or ultimately the associated threat. Avoidance of learnt fear is surprisingly understudied despite its prevalence in pathological anxiety. The current overview proposes potential behavioral mechanisms and neural circuits of avoidance of learnt fear in humans, and discusses findings and paradigms suitable for examining it. Specifically, higher-order conditioning, decision making paradigms, and context-cue conditioning investigate distinct forms of avoidance of learnt fear. We also discuss the clinical prospects and future directions of research in avoidance of learnt fear.

1. Introduction

1.1. Defensive behavior

Fear or anxiety is triggered by situations or stimuli that signal threat and in turn motivate different defensive behaviors. Defensive behaviors are typically adaptive responses that prevent imminent threat (see LeDoux & Daw, 2018; Pittig, Wong, Glück, & Boschet, 2020). However, when defensive behaviors become excessive, persist in the absence of threat, or generalize to non-threatening situations or stimuli, such behaviors may become maladaptive. Indeed, maladaptive defensive behaviors are a major pathological feature of anxiety-related disorders (American Psychiatric Association, 2013).

Defensive behaviors have been studied extensively in the past decades. One of the most influential laboratory model for defensive behavior is the fear and instrumental conditioning framework. This framework has been suggested to be a valid laboratory model for the study of functional and dysfunctional fear and defensive behavior acquisition (Beckers, Krypotos, Boddez, Effting, & Kindt, 2013; Krypotos, Vervliet, & Engelhard, 2018). In this framework, a formerly neutral conditioned stimulus (CS) is repeatedly paired with an aversive unconditioned stimulus (US). Consequently, the CS comes to signal threat and thus evokes conditioned fear. In a following instrumental learning phase, performing a designated response prevents or terminates the US. Depending on how the response effects the status of the US or the CS, defensive behaviors can be classified as *escape* or *avoidance*. The terminology of these responses may seem overlapping, thus it is vital to establish distinct terminology for each response. We therefore highlight the differences between the different types of responses.

1.2. Escape

Escape is defined as responses that terminate exposure to an ongoing US (US-escape[1]) or terminate exposure to an ongoing CS which in turn prevent an upcoming US (CS-escape). CS-escape has received much research attention in non-human animals and is typically examined in a so-called escape-from-fear paradigm. This paradigm is highly similar to the aforementioned fear and instrumental conditioning framework,

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[1] US-escape, defined as response that terminates exposure to an ongoing US, is not discussed here given it is typically adaptive.

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characterized by the termination of CS presentation (and the US it signals) by executing a designated escape response (Amorapanth, LeDoux, & Nader, 2000; Cain & LeDoux, 2007; McAllister & McAllister, 1971; see Fig. 1a). The acquisition of CS-escape is thought to be reinforced by the removal of a feared CS: the termination of the CS reduces conditioned fear, negatively reinforcing CS-escape (Hull, 1943; Mowrer, 1960).

CS-escape is of clinical importance, as it provides insights into how clinically anxious individuals escape from feared situations or stimuli. For instance, a socially anxious individual may leave a conversation (i.e., response that terminates a CS) to prevent humiliation (US). Despite the clinical significance of CS-escape, it will not be covered in detail in the current review as our focus is on avoidance responses (excellent overviews on CS-escape paradigms can be seen in LeDoux & Daw, 2018; LeDoux, Moscarello, Sears, & Campese, 2017; McAllister & McAllister, 1991).

1.3. Avoidance

Avoidance refers to responses that prevent a feared or threatening stimulus. Unlike escape responses, avoidance does not terminate exposure to any ongoing stimulus. Depending whether an avoidance response prevents a threat (US) or even the feared stimulus (CS), avoidance can be categorized into safety behavior or avoidance of learnt fear.

1.3.1. Safety behavior

Safety behavior refers to behavioral responses that prevent (or greatly reduce) a threat when confronting a situation or stimulus that signals threat. Safety behavior is typically adaptive when it effectively reduces threat. For instance, wearing a seatbelt is adaptive given that it significantly reduces serious injuries in vehicle accidents. Safety behavior in anxiety-related disorders is, however, oftentimes maladaptive given the high cost of execution and its persistence in the absence of realistic threat (Pittig et al., 2020).

Safety behavior has been studied extensively in the laboratory via a fear and avoidance conditioning framework. In this framework, after acquiring conditioned fear to the CS, performing a designated response during CS presentation effectively prevents the US. Thus, this behavioral response is referred to as "US-avoidance" given it *prevents US occurrence* (see Fig. 1b). Importantly, despite both CS-escape and US-avoidance prevent US occurrence, US-avoidance does not necessarily terminate CS presentation, thus rendering it qualitatively different from CS-escape. Furthermore, US-avoidance is thought to be driven by US omission (Lovibond, 2006; Seligman & Johnston, 1973) or positively reinforced by the presence of safety signals after executing US-avoidance (e.g., Fernando, Urcelay, Mar, Dickinson, & Robbins, 2014; Morris, 1974), whereas CS-escape is thought to be predominantly driven by negative reinforcement linked to CS termination (Dinsmoor, 1954; Schoenfeld, 1950).

Fear conditioning research has substantially contributed to our understanding of dysfunctional safety behaviors. Numerous studies found the persistence of US-avoidance even when it becomes costly (e.g., Claes, Karos, Meulders, Crombez, & Vlaeyen, 2016; Pittig, 2019; Rattel, Miedl. Blechert, & Wilhelm, 2017; van Damme, Van Ryckeghem, Wyffels, van Hulle, & Crombez, 2012). Compared to low-cost US-avoidance (in which cost or effort for executing US-avoidance is minimal), incorporating a cost into US-avoidance arguably increases face validity (Krypotos et al., 2018), as it parallels to maladaptive costly safety behavior commonly observed in anxiety-related disorders. Interestingly, costly US-avoidance may also enhance diagnostic validity, as preliminary evidence revealed that clinically anxious individuals were more likely to engage in costly US-avoidance than healthy controls, even in the absence of threat (Pittig, Boschet, Glück, & Schneider, 2021).

Laboratory studies also found a reduction in anticipatory fear to the fear-related CS after executing US-avoidance (Pittig, 2019; Rattel, Miedl, Blechert, & Wilhelm, 2017; Wong & Pittig, 2021). This parallels the reduction of fear after engaging in safety behavior when confronting fear-related situations or objects. US-avoidance also generalizes to other generalization stimuli (GSs) that perceptually (e.g., Meulders, Jans, & Vlaeyen, 2015; San Martin, Jacobs, & Vervliet, 2020; van Meurs, Wiggert, Wicker, & Lissek, 2013) or conceptually (e.g., Boyle, Roche, Dymond, & Hermans, 2016; Dymond, Roche, Forsyth, Whelan, & Rhoden, 2007; Dymond, Schlund, Roche, & Whelan, 2014) resemble the CS. Thus, a wide range of stimuli that resemble the fear-related CS are able to evoke US-avoidance.

Furthermore, laboratory studies suggested that excessive engagement with US-avoidance precludes extinction learning to the fear-related CS, that is, protecting one from learning that the CS no longer signals an US (protection from extinction; see Section 5 for more details). The pathological characteristic of excessive US-avoidance is exacerbated with laboratory findings showing the persistence of US-avoidance after response-prevention extinction learning (Klein, Shner, Ginat-Frolich, Vervliet, & Shechner, 2020; Krypotos & Engelhard, 2018; van Uijen, Leer, & Engelhard, 2018; Vervliet & Indekeu, 2015).

Collectively, there are ample laboratory studies examining the acquisition of safety behavior and its interaction with conditioned fear within a fear and avoidance conditioning framework. While there are still important future directions (Pittig et al., 2020), these studies provide insights into how safety behavior gains its pathological quality in anxiety-related disorders.

1.3.2. Avoidance of learnt fear

Avoidance of learnt fear is another form of fear-related avoidance. It refers to avoidance to situations or stimuli that signal a fear-related stimulus. This means, a behavioural response that *prevents the occurrence of a feared stimulus or situation itself*. Clinical evidence showed that individuals with anxiety-related disorders not only execute safety behavior when confronting objects of fear, but also actively avoid situations or stimuli that signal the presence of fear-related objects (Nowakowski, Rogojanski, & Antony, 2013). For instance, individuals with PTSD are likely to avoid situations or stimuli that signal the presence of trauma reminders (Ehlers & Clark, 2000; Sareen, 2014). Similarly, individuals with phobias would avoid places or stimuli that signal phobic-related objects (e.g., Katz, 1974; Kleinknecht & Lenz, 1989; Sawchuk, Lohr, Tolin, Lee, & Kleinknecht, 2000; Walz, Mühlburger, & Pauli, 2016). Similar to safety behavior, avoidance of learnt fear becomes pathological when it severely impairs daily life and is not in relation to the actual threat. For instance, clinically anxious individuals reported taking a lengthy detour to avoid places where trauma reminders or feared objects are likely to be encountered (Corrigan, Samuelson, Fridlund, & Thomé, 2007; Walz, Mühlburger, & Pauli, 2016). Thus, it is important to understand the role of avoidance of learnt fear in anxious psychopathology.

In a conditioning framework, avoidance of learnt fear can be operationalized as "*CS-avoidance*" (hereinafter we refer avoidance of learnt fear as CS-avoidance). It refers to behavioral responses that prevent the occurrence of a fear-related CS (Krypotos et al., 2018; Pittig et al., 2020). Conceptually, CS-avoidance is executed upon stimuli or contexts to prevent the upcoming CS (see Fig. 1c). CS-avoidance is unique from US-avoidance and escape responses as it prevents the occurrence of both CS and US, and does not involve the termination of exposure to ongoing threat signal or harm, respectively.

Importantly, CS-avoidance is linked to stimuli or contexts preceding the feared stimulus that have no direct association with the US (e.g., an individual with dog phobia avoids going to a park that is not directly associated with a dog attack). Thus, CS-avoidance seemingly shares a similar mechanism with generalization of avoidance, given that both entail avoidance to stimuli or contexts that have no direct link with the US. However, there is a fine distinction between CS-avoidance and generalization of avoidance. While generalization of avoidance entails a spread of avoidance to GSs that perceptually or conceptually resemble the CS+, these GSs do not necessarily predict the onset of CS+. CS-

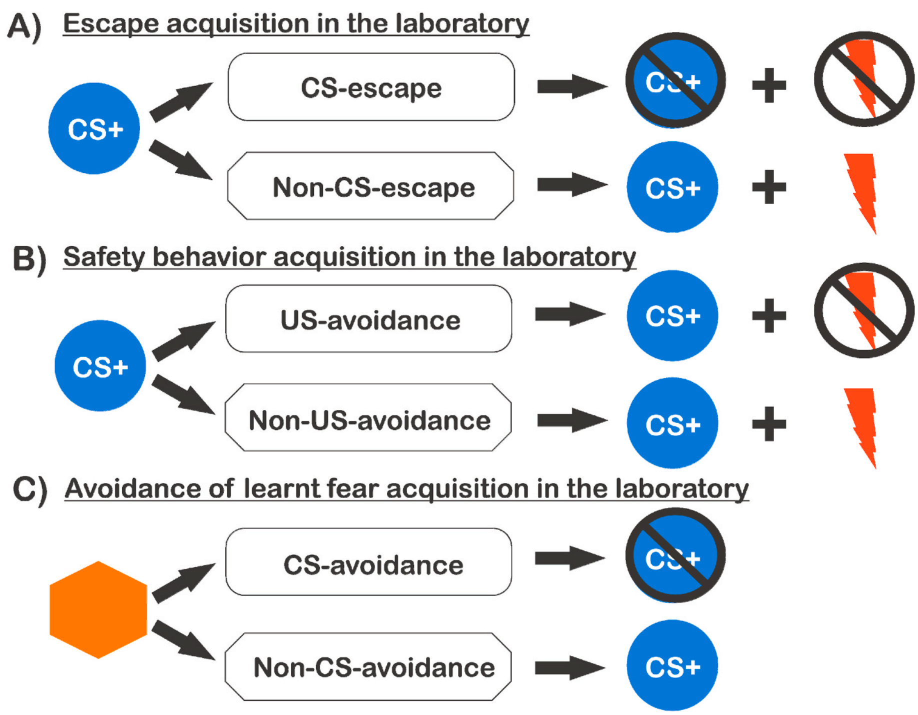

Fig. 1. A) The acquisition of CS-escape in a typical escape-from-fear paradigm. After acquiring CS-US contingency, executing a designated escape response *during CS presentation* terminates the CS and prevents the aversive US that follows. In contrast, not executing the designated escape response leads to persistent CS presentation and US administration. B) The acquisition of safety behavior in a typical US-avoidance paradigm in humans. Executing a designated avoidance response *during CS presentation* prevents the aversive US. In contrast, not executing the designated avoidance response leads to US administration. US-avoidance only prevents the US, but does not terminate CS presentation. C) The proposed acquisition of avoidance of learnt fear in a CS-avoidance paradigm in humans. The hexagon represents a stimulus that signals a fear-related CS. Executing a designated avoidance response *during this stimulus preceding the CS* prevents CS presentation, thus effectively prevents the US. In contrast, not executing the designated avoidance response leads to CS presentation, and the subsequent US is either presented or not depending on the experimental design.

avoidance, on the other hand, entails avoidance to stimuli or contexts that directly signal the onset of CS+. Therefore, CS-avoidance, in its own right, provides a unique account on why clinically anxious individuals avoid a broad range of stimuli or contexts that are seemingly unrelated to their pathogenesis of fear.

In sum, although there is an increasing interest in defensive behavior, in particular avoidance in humans, most studies focused on the acquisition, maintenance and reduction of safety behavior (see Pittig et al., 2020). CS-avoidance, on the other hand, received little attention, despite its potential for providing a unique account of pathological avoidance. It is thus important to further the understanding of CS-avoidance and its underlying mechanisms. CS-avoidance can be further elucidated in highly controlled laboratory paradigms (Richter, Pittig, Hollandt, & Lueken, 2017). The aim of the current article is thus four-fold:

i) Proposing potential behavioral mechanisms of CS-avoidance based on preliminary evidence in humans.
ii) Providing an overview of preliminary fear and avoidance conditioning research on CS-avoidance and discuss paradigms suitable for examining it.
iii) Proposing neural circuits potentially involved in CS-avoidance based on preliminary evidence.
iv) Discussing relevant clinical prospects and future research directions of CS-avoidance.

2. Potential behavioral mechanisms of CS-avoidance

Given the lack of laboratory research in CS-avoidance, the specific behavioral mechanisms are largely unknown. Based on findings on related avoidance research, we propose four potential underlying mechanisms that underlie the acquisition and maintenance of CS-avoidance, namely threat expectancy, safety signal, negative valence, and automatic avoidance tendency.

2.1. CS-avoidance driven by threat expectancy

One intuitive assumption is that CS-avoidance ultimately prevents an US: CS-avoidance not only prevents the CS, but also prevents the subsequent US it signals. Thus, CS-avoidance and US-avoidance may be driven by a common mechanism that serves to prevent the US. Recent studies in humans provided some preliminary evidence to support this notion. In Wong and Pittig (2020), participants were asked to choose between two options on every test trial after differential fear conditioning. One option led to a higher chance of reward, but also signalled the presence of a novel exemplar that belonged to the same category of the CS+ (GS+), whereas another option led to a lower chance of reward but signalled the presence of a novel exemplar of the same category of the CS- (GS-). After choosing one of the options, participants were prompted to indicate their US expectancy ratings to the exemplar presented corresponding to the chosen option. Participants exhibited higher US expectancy ratings to the GS+ than the GS-, indicating fear generalization. US expectancy ratings to the GS+ decreased across non-reinforced test trials due to extinction learning; importantly, this decrease in US expectancies aligned with a decrease in avoidant decision to the option linked to the GS+ (i.e., generalization of CS-avoidance). This pattern suggests that CS-avoidance (and its generalization) was at least partly linked to participants' threat expectancy.

Furthermore, Lemmens, Smeets, Beckers, and Dibbets (2021) employed a novel fear conditioning design that allowed simultaneous investigation of both CS-avoidance and US-avoidance. Participants could choose to avoid a fear-related CS, however, approaching this CS was incentivized by a competing reward. A novel aspect was that participants could still engage in US-avoidance after approaching the CS (i.e., not executing CS-avoidance), which would, however, omit the competing reward. Results showed that when the CS was approached, participants only rarely engaged in a subsequent US-avoidance (27% of trials). This pattern suggests that participants who wanted to avoid an US already engaged in CS-avoidance, whereas those who chose to approach to obtain the competing reward were unlikely to further engage in US-avoidance. High levels of retrospective US expectancy ratings to the CS complemented the notion that CS-avoidance was driven by US anticipation.

These preliminary studies suggest that CS-avoidance may operate on a chain-like structure: engaging in CS-avoidance prevents the CS and the subsequent US it signals. If CS-avoidance is largely driven by threat expectancy, severing the association between the CS and the stimulus preceding it, or extinguishing the CS-US association (CS-extinction) could then reduce CS-avoidance. Preliminary studies in humans (Vansteenwegen, Crombez, Baeyens, Hermans, & Eelen, 2000) found a reduction in conditioned fear to the stimulus that signalled the CS+ after extinguishing the link between these two stimuli. This pattern thus suggests that breaking up this chain may speculatively help reducing CS-avoidance. In a similar vein, if CS-avoidance is purely driven by this chain-like structure characterised by threat anticipation, extinguishing CS-US contingency should also reduce CS-avoidance.

If CS-avoidance is purely driven by US anticipation, then it may be intuitive to assume CS-avoidance as a form of US-avoidance. However, we see CS-avoidance as qualitatively different from US-avoidance, given these two types of avoidance are acquired to and evoked by different stimuli (that is not via stimulus generalization). Thus, future studies examining CS-avoidance should avoid confounding CS-avoidance with US-avoidance.

2.2. CS-avoidance driven by safety signals

The safety signal account (Weisman & Litner, 1972) puts forward the idea that executing US-avoidance would generate some safety signals; these safety signals include interoceptive stimuli (Rescorla, 1968) or proprioceptive stimulations (e.g., tactile stimulation of executing US-avoidance). These safety signals are thought to serve as conditioned inhibitors which positively reinforce US-avoidance (Fernando et al., 2014; Morris, 1974).

The idea of conditioned inhibition may explain the reinforcement of CS-avoidance. CS-avoidance not only prevents CS occurrence, but also the subsequent US that follows. Thus, the absence of an US after executing CS-avoidance combined with the safety signals generated by CS-avoidance align with the safety signal account. That is, these safety signals serve as conditioned inhibitors that reinforce CS-avoidance.

If the safety signal account is accepted as a model that explains the acquisition of CS-avoidance, then severing the link between the CS and its preceding stimulus or extinguishing the CS-US association may not effectively reduce CS-avoidance, given that safety signals drive CS-avoidance.

2.3. CS-avoidance driven by negative valence

Some human fear conditioning studies suggest that CS-avoidance persists even after successful extinction learning to the CS+ (Blechert, Michael, Vriends, Margraf, & Wihelm, 2007; Engelhard, Leer, Lange, & Olatunji, 2014). After fear extinction, participants were more likely to choose a reward that was associated with a CS- over another reward associated with an extinguished CS+, despite both rewards were equally appetitive. Mason and Richardson (2010) also found that visual avoidance to the CS+ persisted even after US expectancies to it had been extinguished. Besides the safety signal account, the persistence of CS-avoidance after CS-extinction could also be due to the acquired negative valence to the CS+ and/or the stimulus that signalled it after fear acquisition (Baeyens, Eelen, & Crombez, 1995; Hermans, Vansteenwegen, Crombez, Baeyens, & Eelen, 2002, 2005). Negative valence, unlike conditioned fear, is typically less affected by extinction learning (see Dirikx, Hermans, Vansteenwegen, Baeyens, & Eelen, 2004). Negative valence per se is also thought to be sufficient to guide avoidance (Chen & Bargh, 1999; Hans Phaf, Mohr, Rotteveel, & Wicherts, 2014; Krieglmeyer, Deutsch, De Houwer, & De Raedt, 2010), even when an aversive US is not expected (see referential account; see Baeyens et al., 1995; De Houwer, Thomas, & Baeyens, 2001). Preliminary studies showed that a stimulus that signalled a CS+ gained negative valence, thus suggesting the possibility that negative valence is involved in driving CS-avoidance (Wong & Pittig, 2022; Yu, Lang, Birbaumer, & Kotchoubey, 2014). However, it is still largely unclear whether CS-avoidance is driven by the negative valence of the stimulus that signals a CS+, negative valence of the CS+, or a combination of both. Future research is required to unravel these potential factors.

2.4. CS-avoidance driven by automatic avoidance tendency

A related mechanism of CS-avoidance is the automatic avoidance tendency acquired to a feared stimulus. Proponents have suggested that fear serves as an emotional disposition for defensive behaviors, for instance, fight or flight (Frijda, 2010; Lang, Bradley, & Cuthbert, 1998; Mauss & Robinson, 2009). In fear conditioning, the acquired fear to the CS+ is proposed to facilitate avoidance, by activating an automatic tendency to avoid. Evidence supportive of this notion (Krypotos, Effting, Arnaudova, Kindt, & Beckers, 2014, 2015) found a tendency to avoid the CS+ even in the absence of any instrumental training. After differential fear conditioning, participants were asked to control a manikin to either approach or avoid the CS+ or the CS-. In congruent trials, participants were instructed to avoid the CS+ (and approach the CS-), whereas in incongruent trials, participants were instructed to approach the CS+ (and avoid the CS-). Participants exhibited faster reaction time to execute the behavioral response on congruent trials than incongruent trials. Specifically, they were faster to avoid the CS+ than to approach the CS+. This pattern was interpreted as fear acquired to the CS+ activating the tendency of avoidance, supporting the idea that fear facilitates avoidance. Interestingly, this avoidance tendency is thought to be activated by conditioned fear to the CS+ regardless of threat expectancy: First, there was no instrumental training of US-avoidance, meaning that participants did not acquire any behavioral responses to prevent an US prior to test. Second, the US electrodes were disconnected during test, thus suggesting that the avoidance tendency was not driven by US anticipation. Empirical studies have shown an increase in fear to a stimulus or context that signals the CS+ (e.g., Baas, Nugent, Lissek, Pine, & Grillon, 2004; Davey & Arulampalam, 1982; Dunsmoor, White, & LaBar, 2011; Siddle, Bond, & Friswell, 1987; van Ast, Vervliet, & Kindt, 2012; Vansteenwegen et al., 2000; see *Section 3* for details). If conditioned fear facilitates avoidance (Frijda, 2010; Lang et al., 1998; Mauss & Robinson, 2009), it is speculated that fear acquired to these CS-predicting stimuli or contexts would evoke a tendency to avoid, driving overt CS-avoidance. Automatic avoidance tendencies may also help to further understand the effects of negative valence. Negative valenced stimuli have been linked to faster avoidance tendencies (Buetti, Juan, Rinck, & Kerzel, 2012; Chen & Bargh, 1999; Eder & Rothermund, 2008). Thus, both mechanisms do not seem to be exclusive, but rather interacting.

In sum, CS-avoidance could be driven by threat anticipation (and its prevention) or reinforced by safety signals generated by CS-avoidance. However, additional mechanisms, such as negative valence or automatic avoidance tendencies, may contribute to CS-avoidance. More empirical studies and experimental models are required for detailed understanding of CS-avoidance.

3. CS-avoidance in fear and avoidance conditioning

In the following, we will briefly review different paradigms suitable for examining distinct forms of CS-avoidance, namely higher-order conditioning, decision making paradigm, and context-cue conditioning. As research in humans is oftentimes preliminary, we will briefly review research in non-human animals, before reviewing preliminary evidence in humans for each paradigm.

3.1. CS-avoidance in higher-order conditioning paradigms

In higher-order conditioning paradigms, conditioned responses could be evoked by a stimulus that has direct association with the CS+, but has no direct association with the US (Gewirtz & Davis, 2000). Higher-order conditioning could be typically categorized into sensory preconditioning and second-order conditioning.

3.1.1. Sensory preconditioning

In sensory preconditioning, a neutral CS is repeatedly paired with another neutral CS, with the latter afterwards paired with an US. The latter CS represents a first-order CS and the former a higher-order CS. The higher-order CS comes to evoke conditioned responses, despite not directly associated with the US (Brogden, 1939; Pfautz, Donegan, & Wagner, 1978; Rizley & Rescorla, 1972). This evoked conditioned response can be explained by stimulus-stimulus associations: the higher-order CS activates the representation of the first-order CS, which in turn activates US representation (Gewirtz & Davis, 2000). Alternatively, higher-order cognitive accounts propose that the higher-order CS signals an ultimate anticipation of an US, therefore evoking anticipatory responses (see Boddez, Moors, Mertens, & De Houwer, 2020; Mitchell, De Houwer, & Lovibond, 2009).

Sensory preconditioning in the aversive domain has been primarily investigated in non-human animals. Typically, the higher-order CS was found to evoke conditioned fear (e.g., Holmes, Parkes, Killcross & Westbrook, 2013; Prewitt, 1967; Tait, Marquis, Williams, Weinstein, & Suboski, 1969; Wong, Westbrook, & Holmes, 2019) or avoidance (Davis & Thompson, 1969; Hoffeld, Kendall, Thompson, & Brogden, 1960). The latter could be seen as CS-avoidance as the avoidance response prevents CS presentation.

Sensory preconditioning studies in humans, especially in the aversive domain, are scarce. Nonetheless, similar to non-human animal studies, humans exhibited conditioned fear to a higher-order CS that signalled the fear-related first-order CS+ (Dunsmoor et al., 2011; Vansteenwegen et al., 2000). In addition, Declercq and De Houwer (2009) found that a button press that prevented an aversive US during first-order CS presentation transferred to a higher-order CS that signalled the first-order CS. In other words, the presence of a higher-order CS evoked an avoidance response that had previously prevented an US. This avoidance response also generalized to novel stimuli that perceptually resembled the higher-order CS (Cho & Mitchell, 1971).

3.1.1.1. Precautions of examining CS-avoidance in sensory preconditioning. It is intuitive to interpret the conditioned fear evoked by a higher-order CS via stimulus generalization (i.e., fear generalizes from the first-order CS to the higher-order CS). However, a higher-order CS evoked little to no conditioned responses if it was not paired with the first-order CS prior to first-order CS-US pairings (e.g., Prewitt, 1967; Rizley & Rescorla, 1972). Thus, sensory preconditioning cannot be simply explained by stimulus generalization.

Furthermore, preliminary human studies found that US-avoidance acquired to a first-order CS transferred to a higher-order CS (Declercq & De Houwer, 2009), or to other stimuli that were perceptually similar to the higher-order CS (Cho & Mitchell, 1971). These findings precluded any interpretation of CS-avoidance given that avoidance was acquired to the CS+ (i.e., US-avoidance) which then generalized to other GSs. Indeed, these findings were highly similar to symbolic generalization of US-avoidance (Dymond, Schlund, Roche, De Houwer, & Freegard, 2012; Dymond et al., 2014; Dymond et al., 2011). These studies employed a matching-to-sample task, in which a neutral stimulus (A1) was presented alongside a set of comparison stimulus ([B1, B2, B3] or [C1, C2, C3]. Choosing B1 or C1 in the presence of A1 was reinforced by corrective feedback, thereby associating A1 with B1 and C1. B1 was then paired with an aversive US, followed by the acquisition of US-avoidance to B1. Dymond et al. (2011, 2012, 2014) found that such US-avoidance generalized from B1 to A1 and C1, despite A1 and C1 had no direct association with the US, thus indicating a symbolic generalization of US-avoidance. Therefore, to examine CS-avoidance in a sensory preconditioning paradigm, future studies have to ensure that *the acquisition of avoidance is restricted to the higher-order CS* (see Wong & Pittig, 2022). This allows any avoidance responses to the higher-order CS to be clearly interpreted as CS-avoidance, precluding it to be confounded with generalization of US-avoidance (see Fig. 2a for an overview of examining CS-avoidance in a sensory preconditioning paradigm).

3.1.2. Second-order conditioning

In second-order conditioning, a first-order CS+ comes to signal threat after repeated pairings with an US. Another neutral stimulus, a so-called second-order CS, is then paired with the CS+. Empirical studies in non-human animals showed that second-order CS was able to evoke conditioned fear (e.g., Holmes, Cai, Lay, Watts, & Westbrook, 2014; Lay, Westbrook, Glanzman, & Holmes, 2018; Rescorla, 1982; Rizley & Rescorla, 1972) and avoidance (Tabone & de Belle, 2011; Topál & Csányi, 1999), despite it had no direct association with the US.

Similar to sensory preconditioning, the ability of a second-order CS to evoke conditioned responses is contingent on the pairing between the second-order CS and the first-order CS+, rather than a by-product of stimulus generalization (Parkes & Westbrook, 2010; Witnauer & Miller, 2011; Yin, Barnet, & Miller, 1994).

Evidence for second-order conditioning in humans is relatively scarce in the aversive domain. Some studies showed that adults (Davey & Arulampalam, 1982; Siddle et al., 1987) and children (Reynolds, Field, & Askew, 2017) acquired conditioned fear to a second-order CS. Interestingly, Wessa and Flor (2007) showed that individuals with PTSD showed enhanced conditioned fear to a second-order CS compared to healthy controls, suggesting a model of the acquisition of excessive fear to cues that signal trauma reminders.

Fear-related avoidance was rarely measured in human second-order conditioning studies. Davey and Arulampalam (1982) instructed one group of participants that a key press during first-order CS+ presentation would prevent the US. This, however, rendered the button press responding as US-avoidance given that participants were explicitly instructed to press the key during first-order CS+ presentation. Another study (Malloy & Levis, 1988) used a serial second-order conditioning procedure, in which a second-order CS was followed by a first-order CS+, which in turn was followed by an US. In a following phase, participants were instructed that pulling a hand-dynanometer would terminate all stimuli. This, however, allowed participants to execute the avoidance response during either the second-order CS or the first-order CS+, confounding CS-avoidance and US-avoidance, respectively.

More recently, Klein, Berger, Vervliet, and Shechner (2021) specifically examined CS-avoidance in a serial second-order conditioning paradigm in humans (cf. Malloy & Levis, 1988). That is, avoidance responses were confined to the presentation of second-order CS. Executing avoidance would prevent all subsequent stimuli. Participants exhibited avoidance more frequently to the second-order CS compared to a CS-, allowing a clear interpretation of the acquisition of CS-avoidance.

3.1.2.1. Precautions of examining CS-avoidance in second-order conditioning procedure. In second-order conditioning, the first-order CS is conventionally unreinforced by an US during pairings of the second-order CS and the first-order CS. This procedure is highly similar to conditioned inhibition (A+, AX-) which may generate inhibitory responding to the second-order CS (Pavlov, 1927; Rescorla, 1973). A recent review (Lee, 2021) suggested to direct participants' attention to the association between the first- and second-order CS, or discourage learning of the association between the second-order CS and the absence of an US, to minimize inhibitory learning to the second-order CS (see Fig. 2a for an overview of examining CS-avoidance in a second-order conditioning paradigm).

3.2. CS-avoidance in decision making paradigms involving approach-avoidance conflict

In approach-avoidance conflict tasks, individuals typically have to decide whether to approach or avoid an option that is associated with both aversive and appetitive outcomes. Decision making in non-human

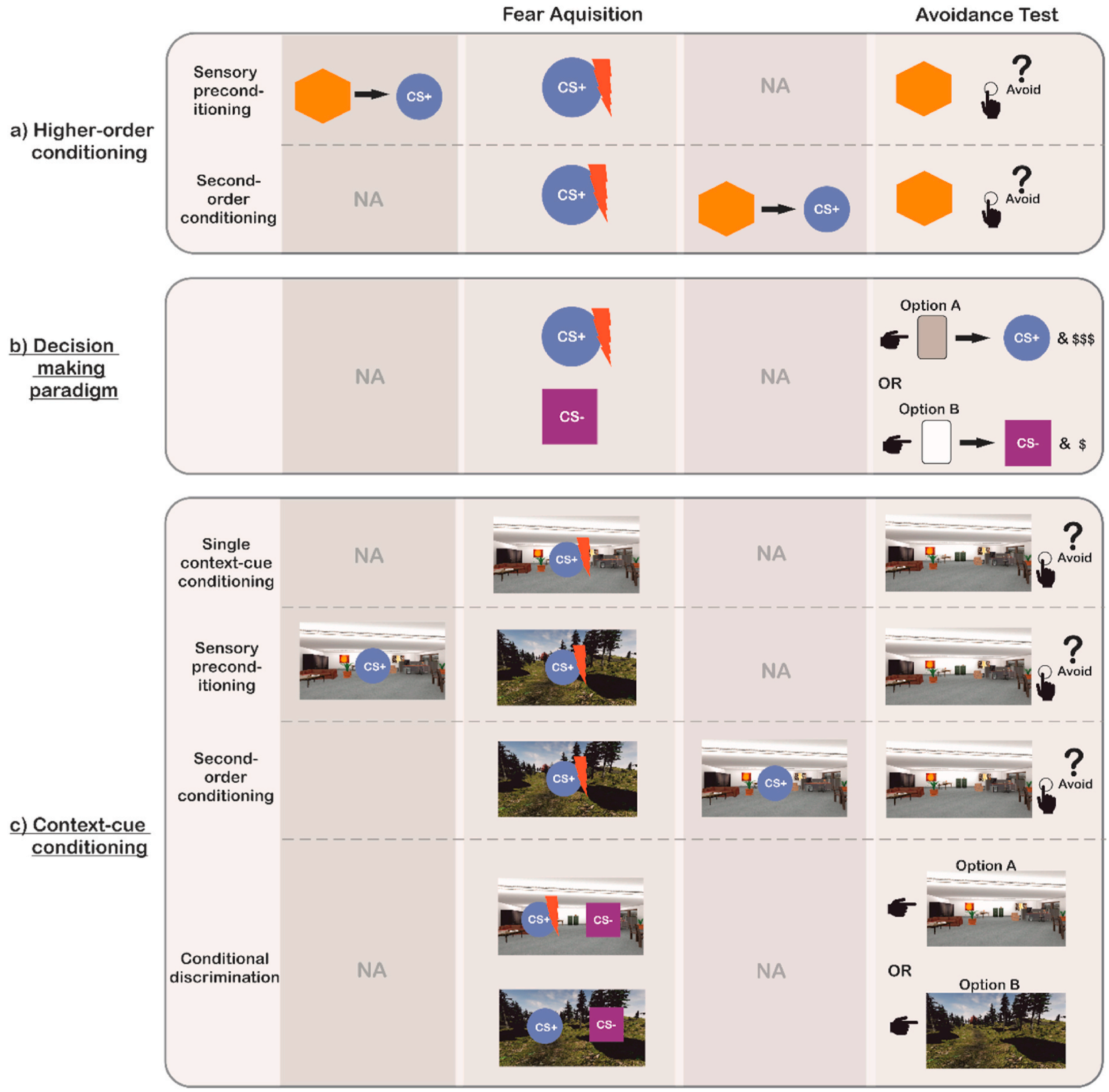

Fig. 2. Graphic depiction of the examination of CS-avoidance in different laboratory paradigms. A) Higher-order conditioning: Hexagon represents a higher-order CS. It signals a first-order CS either before (sensory preconditioning) or after (second-order conditioning) first-order CS-US pairings. In avoidance test, avoidance to the higher-order CS is measured (represented by the button press icon). B) Decision making paradigms involving approach-avoidance conflict: After differential conditioning to the two CSs, two options are given to choose from in the avoidance test: one option is linked to the CS+ and a large amount of reward, whereas another option is linked to the CS- with a small amount of reward. C) Context-cue conditioning: The single context-cue conditioning entails CS-US pairings in a particular context. This context is presented in avoidance test alone, and avoidance responses to it are measured. To prevent the formation of context-US association, context-cue conditioning can be employed via a higher-order conditioning procedure, in which the CS-US pairings occur in a context other than the context in avoidance test. Alternatively, CS-avoidance to a context can be tested in a conditional discrimination task, in which the CS+ signals threat in one context but not the other, whereas the CS- signals safety in both contexts. In avoidance test, both contexts are presented simultaneously and the frequency of choosing each of the context can serve as an indicator of CS-avoidance.

animals had been traditionally investigated in different approach-avoidance conflict paradigms (e.g., Howard & Pollard, 1977; Millan, 2003; Vogel, Beer, & Clody, 1971), laying the foundation for human studies. Despite increasing attention in examining approach-avoidance conflict in humans, the major focus has been the decision to engage in US-avoidance (e.g., Lindström, Golkar, Jangard, Tobler, & Olsson, 2019; Norbury, Kurth-Nelson, Winston, Roiser, & Husain, 2015; Norbury, Valton, Rees, Roiser, & Husain, 2016; Pittig & Scherbaum, 2020; Sierra-Mercado et al., 2015; Talmi, Dayan, Kiebel, Frith, & Dolan, 2009), whereas the investigation in CS-avoidance in similar paradigms received relatively less attention.

Acquisition of CS-avoidance can be examined in the form of avoidant decisions to options linked to a CS+. Pittig, Schulz, Craske, and Alpers (2014) combined fear conditioning with a modified Iowa gambling task (Bechara, Damasio, Damasio, & Anderson, 1994). After differential fear conditioning, participants were asked to choose one of the two decks presented in a gambling task. One deck led to a greater chance of reward, but also signalled the CS+ (high-reward option), whereas another deck led to a lower chance of reward but signalled the CS- (low-reward option). Participants were more likely to choose the low-reward option, at the cost of greater chance to obtain a reward, despite none of the CSs were reinforced in test. This pattern was interpreted as a costly, maladaptive decision to execute CS-avoidance in two ways: first, participants actively avoided choosing the more optimal high-reward option, despite the CS+ that followed was no longer reinforced by an US. Second, persistent avoidant decision to the high-reward option also precluded one from extinction learning to the CS+, leading to protection from extinction (see Section 5). Interestingly, costly avoidant decision also generalizes to novel stimuli categorically related to the CS+ (Wong & Pittig, 2020): participants were more likely to avoid choosing a more optimal, high-reward option that signalled novel stimuli (e.g., dog) belonging to the same category of the CS+ (e.g., mammal; see Fig. 2b for an overview of examining CS-avoidance in a decision making paradigm).

Other decision making studies in humans examined the acquisition of CS-avoidance via a higher-order conditioning paradigm (Gerraty, Davidow, Wimmer, Kahn, & Shohamy, 2014; Luettgau, Porcu, Temelmann, & Jocham, 2021; Rouhani et al., 2019). Two higher-order CSs were paired with two first-order CSs respectively, either via sensory preconditioning (Gerraty et al., 2014) or second-order conditioning (Luettgau, Porcu, Tempelmann, & Jocham, 2021). The higher-order CSs were then presented in a two-alternative-force-choice test. Results showed that the higher-order CS associated with an appetitive CS was preferred over the higher-order CS associated with an aversive CS. Although this pattern could be interpreted as CS-avoidance to a stimulus that signalled an aversive warning signal, it could be alternatively interpreted as CS-approach to a stimulus that signalled an appetitive signal. Using a similar procedure, Rouhani et al. (2019) pitted a higher-order CS that signalled a warning signal against another higher-order CS that signalled a neutral CS. Participants more frequently decided to approach the latter, providing more persuasive evidence for CS-avoidant decisions.

While the aforementioned paradigms primarily investigated the outcome of decision making, other paradigms investigated the process leading to the final decision. For example, we recently adapted a well-established discounting paradigm (see Dshemuchadse, Scherbaum, & Goschke, 2012; Scherbaum, Dshemuchadse, & Goschke, 2012) to examine CS-avoidance (Boschet, Scherbaum, & Pittig, 2021). Preliminary findings showed that the probability of CS+ occurrence had a larger and faster impact during the decision process compared to reward information, suggesting information regarding CS+ plays a major role in deciding the execution of CS-avoidance.

3.3. Context-cue conditioning

Clinically anxious individuals not only avoid discrete stimuli that signal fear-related stimuli, but also situations where the fear-related stimuli are likely to be encountered. In the laboratory, fear and avoidance to situations can be examined in a context-cue conditioning paradigm (Lonsdorf et al., 2017). In this paradigm, a CS is paired with an US in a given context. Specifically, US occurrence is contingent upon the CS, but not to the context where the CS is presented. Thus, this paradigm allows simultaneous assessment of learnt fear to the discrete fear-related CS and the surrounding context (e.g., Baas et al., 2004; Grillon, Baas, Cornwell, & Johnson, 2006).

3.3.1. Contextual fear and CS-avoidance

Using a context-cue conditioning paradigm, it has been well established in rodent studies that not only the discrete CS+ evoked conditioned fear, but also the training context itself (Kim & Fanselow, 1992; Phillips & LeDoux, 1992). Similar to higher-order conditioning, context-cue conditioning allows the examination of CS-avoidance given that the context signals the presence of a fear-related CS. That is, fear and avoidance to the context is evoked via a context-CS association.

Early studies in non-human animals have provided some evidence to support the idea of the formation of a context-CS association. Balay, Capra, Kasprow, and Miller (1982) pre-exposed rodents to a training context. After receiving CS-US pairings in the same context, rodents showed enhanced conditioned suppression to this context alone compared to a novel context alone. The increase in fear responses to the training context was not likely due to a direct context-US association, given that pre-exposure to the training context should have minimized the formation of a context-US association via latent inhibition (Lubow, 1973; Lubow & Moore, 1959). Similarly, in a second-order conditioning study, Helmstetter and Fanselow (1989) found that rodents exhibited stronger conditioned fear to a context that signalled a CS+ compared to another context that signalled a CS-, despite no reinforcement was carried out in neither context. That is, any direct associations between the context and the US were precluded (see also Rescorla [1984, Experiment 2] for a similar study employing a sensory preconditioning paradigm, albeit in an appetitive domain).

Context-cue conditioning paradigm in humans also shed light on the acquisition of fear to the training context. Preliminary studies (Grillon et al., 2006; Hasler et al., 2007; Lonsdorf, Haaker, & Kalisch, 2014) showed heightened retrospective anxiety ratings and EMG startle responses to a context where the CS-US pairings occurred. The heightened conditioned fear to this context is thought to reflect a context-CS association, giving way to the interpretation that the context evokes fear because it signals a fear-related CS.

There is little research in humans on CS-avoidance to a context. Rinck et al. (2016) presented a museum in virtual reality to spider fearful and non-fearful participants. Their task was to find a target painting by walking around this virtual museum. On half of the trials, the target painting was located in a room with spider pictures. Spider fearful participants were less likely to visit these spider rooms compared to non-fearful participants, indicating CS-avoidance to a context that signalled fear-related CSs. Similarly, in a virtual reality Morris water maze task, participants exhibited higher latency to enter the target quadrant where a fear-related CS was located, compared to a control pool where the fear-related CS was absent in the same quadrant (Cornwell, Overstreet, Krimsky, & Grillon, 2013). This pattern indicated passive CS-avoidance to a context that signalled a fear-related CS. In sum, there is some preliminary evidence for CS-avoidance to a context in humans, but more research is required.

Intriguingly, the context can oftentimes set an occasion of whether a CS signals an US or not, that is, context can serve as occasion setters when its presence governs whether an US follows a CS or not (see Holland, 1992; Maren, Phan, & Liberzon, 2013; Trask, Thraikill, & Bouton, 2017). Importantly, seminal studies have showed that occasion setting is unique from simple Pavlovian conditioning, as the occasion setters determine responding to a CS via modulation of the CS-US association instead of forming a direct association with the US (Holland, 1986, 1989; Holland, Lamoureux, Han, & Gallagher, 1999; Holland & Lamarre, 1984; Lamarre & Holland, 1985, 1987).

Inspired by studies examining occasion setting, studies involving conditional discriminative training found that contexts allow the activation of CS-US association or CS-no US association, depending on the history of reinforcement in each context. Two human studies (Baas et al., 2004; van Ast et al., 2012) carried out differential fear conditioning in two contexts: the CS+ signalled an US in one context (threat context) but not in another context (safe context), whereas the CS- was not reinforced in neither context. In test, participants exhibited greater EMG startle responses to the threat context alone compared to the safe context alone. The results suggested that a context signalling a fear-related CS does not always evoke fear (safe context), but only when it renders the CS threatening (threat context). This puts forward the idea that fear to the context could also be acquired via a context-CS′ association, which the apostrophe denotes that the threatening property of the fear-related CS is modulated by the context. This resembles clinically anxious individuals showing less fear to a feared object in a “safe” context (e.g., clinician’s office) but stronger fear outside of a safe context (i.e., dysfunction in contextualization, see Acheson, Gresack, & Risbrough, 2012; Cohen, Liberzon, & Richter-Levin, 2009; Liberzon & Sripada, 2008). Despite preliminary evidence in humans showing that fear to a context can be acquired via a context-CS′ association, more research is required to examine whether CS-avoidance to a context can be acquired via this pathway (see Fig. 2c for an overview of examining CS-avoidance in a context-cue conditioning paradigm).

3.3.2. Precautions of examining CS-avoidance in context-cue conditioning

Fear and avoidance to a context could be acquired via two alternative pathways: direct context-US association and chronic anxiety due to unawareness of stimuli contingencies. Avoidance to a context acquired via these alternative pathways may preclude the interpretation of CS-avoidance to a context.

3.3.2.1. Direct context-US association. The first alternative pathway is the formation of a direct context-US association, meaning that the context evokes fear because it directly signals an US, not because of it signalling a fear-related CS. This precludes any avoidance to the context to be interpreted as CS-avoidance. Indeed, Rescorla (1972) suggested that the context acts as another stimulus that competes with the CS for US association (see also Hull, 1952; Mackintosh, 1974). There are two ways that favour the formation of a context-CS association over a context-US association. First, high CS-US contingency, which refers to a CS reliably signalling an US, is suggested to inhibit the formation of a context-US association (Baker, Mercier, Gabel, & Baker, 1981; Murphy & Baker, 2004; Odling-Smee, 1975; Rescorla & Heth, 1975). Second, close CS-US contiguity, which refers to a close temporal distance between the CS and an US (Pavlov, 1927, 1932), is suggested to inhibit the formation of a context-US association (Odling-Smee, 1978).

3.3.2.2. Awareness of stimuli contingency. A second pathway for the context to evoke apparent fear is determined by the awareness of stimuli contingencies. Grillon (2002) found that participants unaware of the CS-US contingency exhibited greater EMG startle responses to the context during the intertrial intervals compared to the aware participants. This pattern suggests that not being aware of the CS-US contingency leads to a failure to identify safety stimuli (e.g., CS-) and safety periods (e.g., intertrial intervals when the CS+ is absent, see also the safety signal hypothesis, Seligman & Binik [1977]). This leads to a chronic state of anxiety, resulting in an apparent increase in fear to the context. Similarly, studies (Baas, van Ooijen, Goudriaan, & Kenemans 2008; Baas, 2013) found participants who were unaware of stimuli contingencies showed heightened fear to the context, reflecting chronic anxiety due to a failure in identifying safety periods.

Therefore, to examine CS-avoidance to a context, studies should employ experimental parameters that minimize the formation of a context-US association. This could be achieved by entailing high CS-US contingency, close CS-US contiguity, or employing a higher-order conditioning paradigm (cf. Helmstetter & Fanselow, 1989; Rescorla, 1984) which precludes the training context to acquire a direct association with the US. Furthermore, studies can employ verbal instructions that facilitate the awareness of CS-US contingency (see Mertens, Boddez, Krypotos, & Engelhard, 2021) to minimize chronic anxiety to the context due to being unaware of relevant stimuli contingencies.

In summary, we propose that higher-order conditioning paradigms, decision making paradigms involving approach-avoidance conflict, and context-cue conditioning paradigms are well-fitted to examine the distinct forms of CS-avoidance.

4. Neural circuits of fear-related avoidance

The underlying neural circuits of fear-related avoidance have long been studied in rodents. In short, the tripartite circuit consisting of the hippocampus, medial prefrontal cortex (mPFC), and the amygdala, and the circuit's projection to the nucleus accumbens (NAcc), are well accepted to be responsible for the acquisition and expression of fear-related avoidance (Duvarci & Pare, 2014; Fendt & Fanselow, 1999; Janak & Tye, 2015; Killcross, Robbins, & Everitt, 1997; Oleson, Gentry, Chioma, & Cheer, 2012; Ramirez, Moscarello, LeDoux, & Sears, 2015; Sangha, Diehl, Bergstrom, & Drew, 2020). Similar to rodent models, neuroimaging studies in humans found that fear-related avoidance activates the human homolog of tripartite circuit, consisting of the hippocampus, amygdala, and ventral striatum, in addition to the thalamus and orbitofrontal cortex (Bolstad et al., 2013; Eldar, Hauser, Dayan, & Dolan, 2016; Jensen et al., 2003; Kim, Shimojo, & O'Doherty, 2006; Levita, Hoskin, & Champi, 2012; Mobbs et al., 2009; Schlund, Magee, & Hudgins, 2011). However, the neural circuits underlying CS-avoidance are largely unknown to date in both rodent and human models. In the following, we will briefly review the neural circuits in rodents, followed by human imaging studies in the three paradigms reviewed in the previous sections. We then provide some speculations of the potential neural circuits underlying CS-avoidance in humans.

4.1. Neural circuits of higher-order conditioning

Rodent studies in higher-order conditioning have shown that different brain circuits are activated during presentation of a higher-order CS, either before CS+ obtains threat value (i.e., sensory preconditioning) or after CS+ obtains threat value (i.e., second-order conditioning). In sensory preconditioning, the hippocampus and the adjacent perirhinal cortex, but not the basolateral amygdala (BLA), are responsible for associating the neutral higher-order CS and the first-order CS together (Eichenbaum, Otto, & Cohen, 1992; Murray & Bussey, 1999; Nicholson & Freeman, 2000; Talk, Gandhi, & Matzel, 2002; Wimmer & Shohamy, 2011; Winters, Saksida, & Bussey, 2008), and play an important role in transferring the newly learnt value of the first-order CS to the higher-order CS after fear conditioning. In second-order conditioning, both the hippocampus and BLA are responsible for associating a neutral second-order CS with a fear-related first-order CS (Gewirtz & Davis, 1997; Gilboa, Sekeres, Moscovitch, & Winocur, 2014; Parkes & Westbrook, 2010).

Neuroimaging studies in human higher-order fear conditioning are relatively scarce. Strong activation of the left hippocampus was observed when a higher-order CS associated with a fear-related CS was presented in sensory preconditioning (Yu et al., 2014), whereas the anterior hippocampus and amygdala were strongly activated when a second-order CS associated with an aversive CS was presented in second-order conditioning (Luettgau et al., 2021). These findings align with rodent studies in which the hippocampus and amygdala play an important role in higher-order fear conditioning (Gilboa et al., 2014; Parkes & Westbrook, 2010; Talk et al., 2002; Wimmer & Shohamy, 2011).

4.2. Neural circuits in decision making tasks involving approach-avoidance conflict

In rodents, it is well accepted that the ventral hippocampus (vHPC), BLA, mPFC, and ventral striatum modulate avoidance or approach via their inputs to the NAcc (Bannerman et al., 2003; Ito & Lee, 2016; Jinks & McGregor, 1997; Kjelstrup et al., 2002; Shah & Treit, 2003), which controls for the expression of motor behaviour (Bryant & Barker, 2020; Ito & Lee, 2016; Kirlic, Young, & Aupperle, 2017). In particular, the vHPC has been suggested to serve as a behavioural inhibition system when confronted with stimuli of conflicting outcomes (Bannerman et al., 2002; Gray, 1982; Kjelstrup et al., 2002; McHugh, Deacon, Rawlins, & Bannerman, 2004; Padilla-Coreano et al., 2016; Treit & Menard, 1997; Trivedi & Coover, 2004). This system is characterized by its functional heterogeneity in which some subfields promote approach responses whereas other subfields promote avoidance responses (Schumacher et al., 2018; Yeates, Ussling, Lee, & Ito, 2020).

Studies examining the neural circuits of decision making in human approach-avoidance conflict tasks are sparse compared to rodent studies. Preliminary studies showed strong activation of the anterior hippocampus (aHPC) when confronting a conflict in responding (Bach et al., 2014; Loh et al., 2017; O'Neil et al., 2015). In particular, Bach et al. (2014) found that activation of the aHPC was positively associated with threat level, suggesting that the aHPC is involved in monitoring threat level and the subsequent decision in either avoiding or approaching (see also Abivardi, Khemka, & Bach, 2020). These findings align with rodent studies given that the aHPC is the human homolog of vHPC in rodents (Fanselow & Dong, 2010). Of note, other neuroimaging studies (Aupperle & Paulus, 2010; Aupperle, Melrose, Francisco, Paulus, & Stein, 2015; Schlund et al., 2016) found that other downstream regions from the hippocampus, such as the mPFC, amygdala, and NAcc, were also activated during conflict.

4.3. Neural circuits of context-cue conditioning

In rodent models, it is well accepted that the hippocampus is responsible for encoding the context (Fanselow, 2000; Kim & Cho, 2020; Myers & Gluck, 1994) and conveying the representation of the context to the mPFC and amygdala, for the expression of contextual fear (Corcoran & Quirk, 2007; Frankland, Bontempi, Talton, Kaczmarek, & Silva, 2004; Goshen, Brodsky, Prakash, & Deisseroth, 2011; Helmstetter & Bellgowan, 1994; Kim & Cho, 2017; Muller, Corodimas, Fridel, & LeDoux, 1997; Quinn, Ma, Tinsley, Koch, & Fanselow, 2008). In regard to avoidance to a fear-related context, Moscarello and Maren (2018) proposed that the hippocampus activates its downstream projections to the NAcc via the BLA and mPFC, which in turn promotes avoidance.

In humans, preliminary studies found activation of the aHPC, ventral striatum, thalamus, and cerebellum when presented with a context associated with a fear-related CS (Hasler et al., 2007; Lonsdorf et al., 2014), aligning with the neural circuit responsible for the expression of contextual fear in rodents. There is, however, no neural imaging studies on CS-avoidance in context-cue conditioning.

In sum, built on rodent models, preliminary studies in humans suggested that the hippocampus, mPFC, amygdala, and thalamus project their inputs to the NAcc and ventral striatum to express fear-related avoidance. It is speculated that CS-avoidance would be regulated by a similar circuit. Of note, the aHPC in humans plays a pivotal role in associating a higher-order CS with a fear-related CS, monitoring threat level, inhibiting behavioral approach or avoidance when confronting a conflict, and conveying the representation of a context that is associated with a fear-related CS to its downstream projections. Therefore, it is conjectured that the aHPC plays an important role in executing CS-avoidance. Interestingly, some preliminary evidence found that the cerebellum was activated in the presence of a stimulus or context that signalled a fear-related CS (Hasler et al., 2007; Lonsdorf et al., 2014; Yu et al., 2014). Cerebellum is associated with an anticipation of pain (Moulton, Schmahmann, Becerra, & Borsook, 2010; Ploghaus et al., 1999), thus this finding hints toward that CS-avoidance may be at least partly driven by US anticipation.

5. Clinical prospects

Exposure-based therapy is one of the most common and effective treatments for anxiety-related disorders (Craske & Mystkowski, 2006). The reduction of avoidance is a precondition for exposure to be effective (Dymond, 2019; Pittig et al., 2020). This reduction of avoidance entails a decrease in both CS-avoidance and safety behavior (US-avoidance), in which the former allows an individual to confront the stimulus or situation of fear whereas the latter allows an individual to learn that the fear-related stimulus or situation is no longer threatening. In fact, laboratory studies have showed that excessive engagement in US-avoidance during extinction precluded extinction learning to the CS+, leading to "protection from extinction" (Lovibond, Mitchell, Minard, Brady, & Menzies, 2009; Pittig, 2019; Rattel et al., 2017). Protection from extinction due to US-avoidance was traditionally explained via an associative account: the safety signal generated by US-avoidance served as conditioned inhibitors that cancel out the excitatory strength of CS+, thus leading to zero extinction learning. A more recent cognitive account proposes that protection from extinction is due to attributing US omission to the execution of US-avoidance, thus precluding extinction learning (Lovibond, 2006; Lovibond et al., 2009). It is speculated that reducing CS-avoidance is a necessary precursor for reducing US-avoidance and initiates extinction learning. In other words, reducing both CS-avoidance and US-avoidance are pivotal to minimize protection from extinction (see Fig. 3 for the laboratory and clinical models).

Furthermore, strategies on reducing CS-avoidance may have varying effects, depending on the underlying mechanisms that drive CS-avoidance. For instance, if CS-avoidance is largely driven by the ultimate anticipation of a threatening outcome, strategies that rely on reconstructing threat beliefs combined with exposure-based sessions may be more effective in decreasing CS-avoidance.

Other interventions may be suitable if CS-avoidance is largely driven by the negative emotions (e.g., emotional distress, negative valence) associated with the fear-related stimulus regardless of its status of threat predictiveness (see referential account, Baeyens et al., 1995; De Houwer et al., 2001). For instance, acceptance-commitment therapy (Hayes, Strosahl, & Wilson, 2003) may be more effective in reducing CS-avoidance by educating clinically anxious individuals to embrace with the emotional distress associated with the feared stimulus. Alternatively, treatments can incorporate techniques of counterconditioning. In contrast to standard fear extinction which a non-reinforced CS+ was presented repeatedly, counterconditioning involves a CS+ that is repeatedly paired with an appetitive outcome. Empirical findings have shown that counterconditioning can more effectively alleviate negative valence of the CS+ and minimize return of fear (Dirikx et al., 2004; Engelhard, Leer, Lange, & Olatunki, 2014; Zbozinek, Holmes, & Craske, 2015; Hofmann, De Houwer, Perugini, Baeyens, & Crombez, 2010; see also Keller, Hennings, & Dunsmoor [2020] for a review; but see Pittig et al., 2020; van Dis, Hagenaars, Bockting, & Engelhard, 2019). Counterconditioning is also more effective in reducing US-avoidance to the CS+ compared to standard fear extinction (Dour, Brown, & Craske., 2016; Newall, Watson, Grant, & Richardson, 2017; Reynolds et al., 2017).

In a similar vein, US revaluation after conditioning was found to have an impact on CS valence (De Houwer et al., 2001). In particular, pairing an aversive US with stimuli of positive valence after conditioning reduced the negative valence of both the US and CS (e.g., Baeyens, Eelen, Van den Bergh, & Crombez, 1992; Walther, Gawronski, Blank, & Langer, 2009). In the clinical context, US revaluation may, for example, be achieved with cognitive restructuring in cognitive-behavioral therapies, which involves challenging and re-evaluating the feared outcome (Marks, Lovell, Noshirvani, Livanou, & Trasher, 1998; Mueser et al., 2015). Thus, if CS-avoidance is largely driven by the negative valence of the CS+ or the CS-predicting cues, then implementing techniques of counterconditioning or US revaluation in a clinical context may boost reduction of CS-avoidance.

In sum, we speculate that a reduction of CS-avoidance is necessary for exposure-based therapies to take place. However, it is still largely unknown whether CS-avoidance would lead to protection from extinction, or which treatment (or a combination of treatments) can most effectively reduce CS-avoidance. Future research is required to further the understanding of CS-avoidance in a clinical setting and its clinical implications.

6. Future directions

Collectively, CS-avoidance is a maladaptive behavior commonly observed in anxiety-related disorders. It provides a unique account for explaining avoidance to a wide range of stimuli or contexts, which is distinct from the generalization of safety behavior. Its reduction is deemed as a necessary precursor prior to the reduction of fear and safety behavior to a fear-related stimulus. In sum, the reviewed studies tentatively hint at a unique role of CS-avoidance, which, however, remains speculative in numerous ways. Therefore, much future research is required to address these gaps. Perhaps future research on CS-avoidance should prioritized on establishing the groundwork of the acquisition of CS-avoidance, given the little research on it (e.g., Klein et al., 2021;

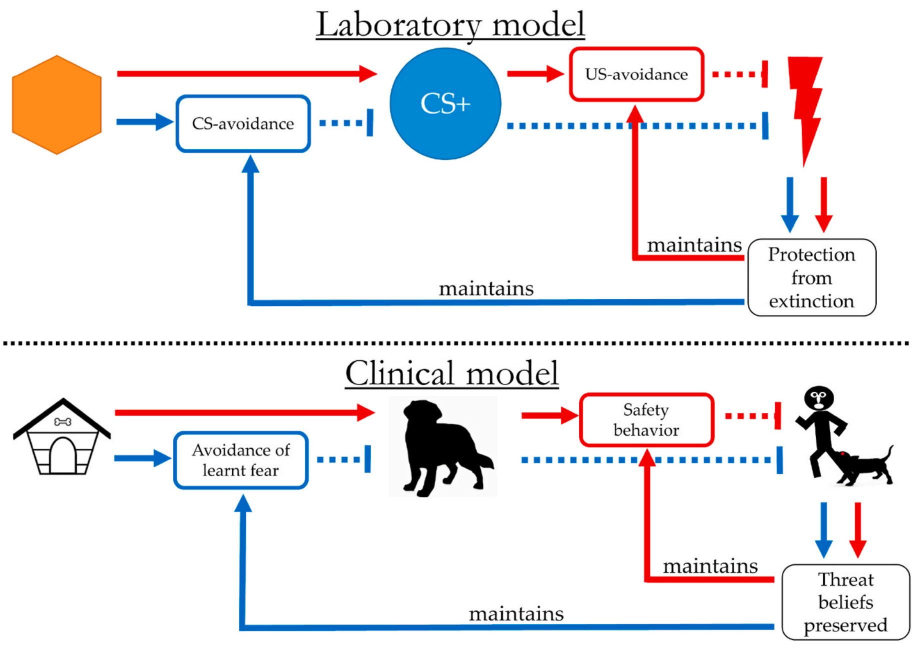

Fig. 3. CS-avoidance and US-avoidance in the laboratory, and their clinical analog to avoidance of learnt fear and safety behavior, respectively. Blue lines represent the pathway of CS-avoidance (avoidance of learnt fear), whereas red lines represent the pathway of US-avoidance (safety behavior). Solid lines represent an outcome or behavior that follows the preceding stimulus or behavior; whereas dotted lines represent an outcome or behavior prevented by the preceding stimulus or behavior. Both CS-avoidance and US-avoidance prevent threat occurrence, precluding extinction learning when the CS is no longer reinforced. This leads to protection from extinction, analog to the preservation of maladaptive threat beliefs. See the color version of this figure online.

Lemmens et al., 2021; Pittig et al., 2014; Wong & Pittig, 2022). We have discussed three potential paradigms within a fear conditioning framework, including higher-order conditioning, decision making paradigms, and context-cue conditioning. Future research can utilize these paradigms to examine the acquisition of CS-avoidance. Furthermore, much research is required in improving our understanding on the behavioral mechanisms and neural circuits underlying CS-avoidance.

Besides the aforementioned gaps in the literature, there are also multiple exciting avenues for future research in CS-avoidance. First, future research can examine whether the distinct mechanisms of safety behavior operate similarly on CS-avoidance. There has been a wealth of research in the distinct mechanisms of safety behavior (see Pittig et al., 2020). For instance, the generalization of safety behavior has been well-documented (Arnaudova, Krypotos, Effting, Kindt, & Beckers, 2017; Cameron, Schlund, & Dymond, 2015; Dymond et al., 2011; Dymond et al., 2014; Hunt, Cooper, Hartnell, & Lissek, 2019; van Meurs et al., 2013), demonstrating that safety behavior generalizes to novel stimuli that perceptually or conceptually resemble the fear-related stimulus. Preliminary evidence suggests that CS-avoidance generalizes to other novel stimuli that conceptually resemble the CS+ (Wong & Pittig, 2020). Recently, there has been an increase in research on the acquisition of habitual safety behavior. It has been demonstrated that repetitively executing a goal-directed response, for instance, safety behavior that aims to prevent a threatening outcome, could transform into habitual responses (Balleine & Dickinson, 1998; Balleine & O'Doherty, 2010), which become insensitive to goal devaluation (Balleine & O'Doherty, 2010; Dayan & Niv, 2008; Dolan & Dayan, 2013; Wood & Runger, 2016). Laboratory studies have demonstrated the acquisition of habitual safety behavior in healthy samples (e.g., Flores, Lopez, Vervliet, & Cobos, 2018; Glück, Zwosta, Wolfensteller, Ruge, & Pittig, 2021) and clinical samples (Gillan et al., 2014). However, it is largely unknown whether CS-avoidance could become habitual. Furthermore, research has focused on the impact of relief on safety behavior. Relief refers to a pleasant affective state induced by the removal of an expected negative outcome (Roseman, 1996; Roseman, Spindel, & Jose, 1990). Preliminary studies have showed that executing safety behavior led to an increase in relief ratings (San Martin et al., 2020; Vervliet, Lange, & Milad, 2017), which the relief experienced after US omission is suggested to further reinforce safety behavior. It is largely unknown whether these distinct mechanisms would also apply to CS-avoidance. Future research is required to examine these distinct mechanisms on CS-avoidance.

Second, future research can examine whether factors that have an impact on safety behavior would also affect CS-avoidance in a similar way. Laboratory studies have found multiple factors that either directly or indirectly enhance or dampen safety behavior (see Pittig et al., [2020] for a review). For instance, vulnerability individual traits such as trait anxiety (Gorka, LaBar, & Hariri, 2016; Pittig & Scherbaum, 2020) and intolerance of uncertainty (Flores et al., 2018; Hunt et al., 2019), and external factors such as acute stress (e.g., Vogel & Schwabe, 2019) are associated with enhanced safety behavior. In contrast, resilient individual traits such as distress tolerance (Vervliet et al., 2017) and sensational seeking (Rattel et al., 2020), and external factors such as the cost of executing safety behavior (e.g., Pittig, 2019; Rattel et al., 2017; van Meurs et al., 2013; Wong & Pittig, 2021) are associated with a decrease in safety behavior. Of note, we have recently found that low-cost per se motivates the execution of safety behavior (Wong & Pittig, 2021). Therefore, we suggest future research to incorporate a cost in CS-avoidance, which also increases the diagnostic validity of avoidance (Krypotos et al., 2018).

Third, future research can examine whether interventions that reduce safety behavior would also reduce CS-avoidance to a similar extent. As mentioned previously, certain factors serve to dampen safety behavior, therefore enabling extinction learning to take place (Pittig et al., 2020). For instance, incorporating financial incentives (e.g., Pittig, 2019; Wong & Pittig, 2021) or social incentives (Pittig, Hengen, Bublatzky, & Alpers, 2018; Pittig, Treanor, LeBeau, & Craske, 2018) for behavioral approach, or mere verbal instructions or observation to initiate approach (Pittig & Wong, 2021) could effectively reduce safety behavior. Interestingly, Bennett et al. (2020) recently found that installing behavior that competed with safety behavior greatly reduced safety behavior generalization. Thus, it is speculated whether these interventions would also reduce CS-avoidance.

7. Conclusion

In the past decade, research on fear-related avoidance has greatly furthered the understanding of the acquisition and maintenance of pathological avoidance in anxiety-related disorders, and the different interventions to reduce it. However, much research focused on safety behavior, while CS-avoidance received little attention despite its unique role and clinical importance in anxiety-related disorders. In this article, we propose the potential underlying mechanisms of CS-avoidance, and review preliminary evidence of CS-avoidance and paradigms suitable for examining it, namely higher-order conditioning, decision making, and context-cue conditioning. These paradigms allow the investigation of CS-avoidance in the form of avoidance responses to stimuli or contexts that signal a CS, or avoidant decision to an option linked to the CS. We also discuss some pitfalls for examining CS-avoidance (e.g., confounding CS-avoidance with US-avoidance), and methods to minimize such issues. Future experimental research focusing on the underlying behavioral mechanisms and neural circuits of CS-avoidance, and factors that either directly or indirectly amplify or dampen CS-avoidance (e.g., vulnerable or resilient individual traits) is much required.

CRediT authorship contribution statement

Alex H.K. Wong: Conceptualization, Funding acquisition, Visualization, Writing – original draft. **Franziska M. Wirth:** Conceptualization, Visualization, Writing – review & editing. **Andre Pittig:** Conceptualization, Funding acquisition, Visualization, Supervision, Writing – review & editing.

Declaration of competing interest

None.

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