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# The validity of human avoidance paradigms

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ABSTRACT

Excessive avoidance towards innocuous cues is a central diagnostic criterion across anxiety-related disorders. Relevant laboratory paradigms typically include instrumental learning procedures, where the presentation of an aversive cue (e.g., a shock) can be prevented by executing an experimenter-defined response (e.g., a button press) during the presentation of a warning cue (e.g., a square). Despite the popularity of these paradigms, there is no evaluation of how well the experimental findings of conditioned avoidance extend to maladaptive avoidance, or whether findings from animal studies could be informative for human studies. Here, we present a validation of the conditioned avoidance paradigm. We show that although this procedure meets the majority of the tested validity criteria (i.e. face, construct, predictive, and diagnostic validity), it also faces a number of challenges, including the non-consideration of individual differences in learning or the use of procedures that cannot be easily translated to clinical settings. For meeting these challenges, we suggest extensions of the paradigm including the test of individual differences by using ambiguous stimuli as well as the use of virtual reality procedures. Our main conclusion is that despite the significant knowledge provided in conditioned avoidance paradigms, their expansion will allow reaching more theoretical and clinical insights.

Although in case of impending threat avoidance is useful for the organism's survival, excessive avoidance of relative safe cues (e.g., house spiders) or situations (e.g., group gatherings or exercising) can have a severe impact on individuals' everyday functioning. Indeed, such avoidance behavior is recognized as a fundamental symptom across many mental disorders, such as anxiety disorders and post-traumatic stress disorder (American Psychiatric Association, 2013). Despite its key role in *adaptive* and *maladaptive* functioning, most of the experimental and clinical insights of how avoidance is acquired and maintained are based on studies that were published until the decade of 1970s. To date, there is a surge of interest in the acquisition and reduction of avoidance (Hofmann & Hay, 2018; LeDoux, Moscarello, Sears, & Campese, 2017; Pittig & Scherbaum, 2018; see also special issues in Behavior Research and Therapy edited by; Beckers & Craske, 2017, and Frontiers in Behavioral Neuroscience edited by; Servatius, 2016). This resurgence of interest provides hope that some key questions about avoidance learning may eventually be answered, such as why some individuals express maladaptive avoidance after a traumatic event whereas some others do not.

Behavioral avoidance[1] has traditionally been tested by using conditioned *avoidance tasks* (AvT). When applied in humans, this paradigm usually entails two phases: a *Pavlovian* and an *Instrumental* phase (see Fig. 1) (e.g., Lovibond, Mitchell, Minard, Brady, & Menzies, 2009). In the Pavlovian phase, an inherently neutral stimulus (e.g., a picture of a square or a sound; Conditional Stimulus or CS) is paired with an aversive stimulus (e.g., electric stimulation; Unconditional Stimulus or US). This procedure typically results in the CS eliciting fear responses and threat expression (e.g., higher skin conductance responses) in anticipation of the US. In the Instrumental phase, the US may be canceled by the performance (*active avoidance*) or inhibition (*passive avoidance*), of an experimenter-defined response (e.g., a button press) during the CS presentation. Usually, participants perform the experimenter-defined response upon the CS presentation. Although AvT had been traditionally used in rodents, dogs, or pig studies (e.g., Mowrer & Lamoreaux, 1942; Solomon & Wynne, 1953), to date, more and more studies use human participants (see Fig. 2).

By using AvTs, knowledge of the basic cognitive processes of adaptive avoidance has been achieved. To illustrate, Lovibond, Saunders, Weidemann, and Mitchell (2008) have provided evidence that US-avoidance during CS presentation is mediated by the expectancy of a US occurring. This finding challenged influential models of avoidance acquisition according to which avoidance is mediated by

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[1] Throughout our article we refer to behavioral avoidance, and not to other types of avoidance (e.g., cognitive avoidance) that are commonly addressed with different experimental paradigms than the ones discussed here.

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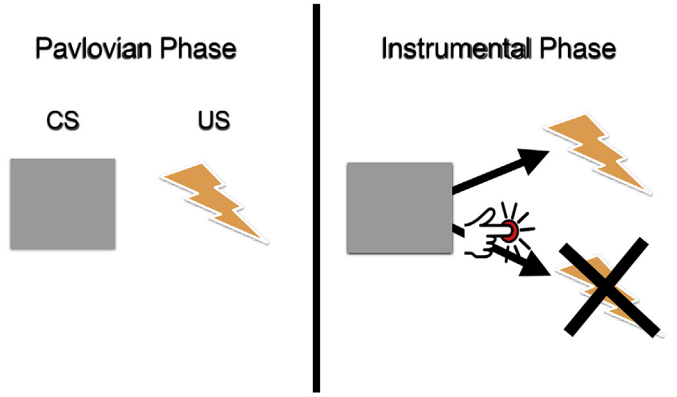


**Fig. 1.** Graphical depiction of the AvT procedure. Left panel: Pavlovian phase. During this phase participants learn to associate a CS, here a square, with the presentation of an aversive US, here a shock. Right panel: Instrumental phase. During this phase the CS is followed by a US unless a participant evokes an experimenter-defined response, here a button press, which cancels the US.

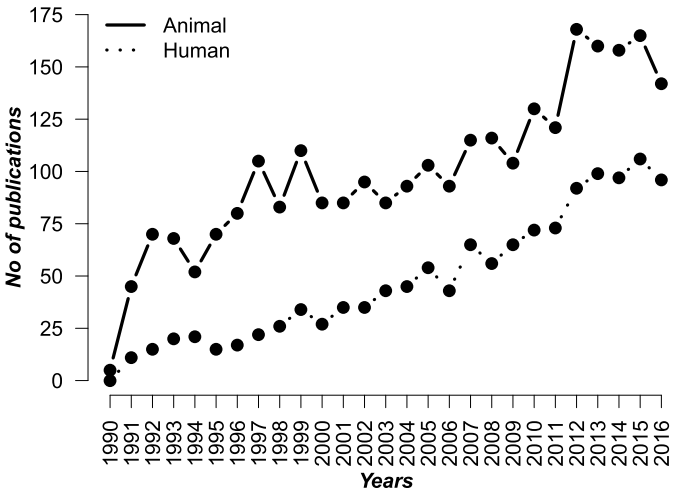


**Fig. 2.** Number of publications indexed in Thomson Reuters' Web of Science for the research areas of psychology, psychiatry, and neuroscience in which "avoidance" and "animal" or "humans" was included in their title, by year 1990–2016 (as of May 02, 2017).

fear reduction (e.g., two-factor theory; Mowrer, 1956). Also, Dymond, Roche, Forsyth, Whelan, and Rhoden (2007, 2008) have elegantly shown that participants exhibit avoidance not only to the CSs that were used in avoidance training, but also to other stimuli that had previously been associated with the CS and not directly with avoidance responses. We have also provided evidence that avoidance, reflex-like, tendencies towards a CS can be expressed after Pavlovian conditioning, without influence of an instrumental procedure (Krypotos, Arnaudova, Effting, Kindt, & Beckers, 2015; Krypotos, Effting, Arnaudova, Kindt, & Beckers, 2014).

Lastly, the relevant neuro-correlates of avoidance learning have been primarily tested in rodent studies. These studies have underlined the central role of amygdala (which is argued to hold the CS information), infralimbic prefrontal cortex (which suppresses freezing to the CS), and the nucleus accumbens (which supports CS-related actions; e.g., avoidance) (see LeDoux et al., 2017, for a review).

Apart from elucidating the relevant cognitive and neurological mechanisms, AvTs are nowadays also used as experimental parallels of how maladaptive avoidance is acquired in clinical populations (Bouton, 2000; Mineka & Zinbarg, 2006). Specifically, and by following the reductionism logic of the paradigms used in the experimental psychopathology, it can be argued that similarly to how participants will learn to press a computer key after seeing a CS, individual with anxiety symptomatology may start avoiding phobic-related situations (e.g., going to the gym in case of panic patients). AvT are currently also used to test novel interventions for reducing avoidance (see below). Finding a way to reduce the rate of avoidance during the CS presentation could be a building block for subsequent translational studies that could develop a therapeutic protocol based on the experimental procedure (e.g., Treanor & Barry, 2017; van Uijen, Leer, & Engelhard, 2018; Vervliet & Indekeu, 2015; Vervliet, Lange, & Milad, 2017). This last line of research is particularly important clinically. As maladaptive avoidance is a cardinal characteristic across anxiety and stress-related disorders (American Psychiatric Association, 2013), elucidating the working mechanisms of such avoidance could prove invaluable in battling these disorders.

Despite their importance in the current experimental and clinical research, a formal validation of AvTs is not yet available. Specifically, although AvTs are routinely used for measuring conditioned avoidance, it has not been addressed whether the relevant findings could be generalized to maladaptive avoidance. In case AvT addresses merely adaptive, rather than maladaptive, responding towards predictors (the CS) of aversive events (the US), then they could be better used to test the (neuro)cognitive mechanisms and neural underpinnings of adaptive avoidance only. It is also unclear how close the human learning version of the AvT is to the animal version and as such how readily findings can be translated between the different species. Please note that the above considerations apply also to other paradigms used in the field of experimental psychopathology as even in well-established experimental paradigms (e.g., see Scheveneels, Boddez, Vervliet, & Hermans, 2016), there is always a translational gap between laboratory models and the disorder of interest (Luyten, Vansteenwegen, van Kuyck, Gabriëls, & Nuttin, 2011; Vervliet & Raes, 2013); this calls for a formal validation of any model used in psychopathology research.

Given the renewed interest in the study of avoidance and its principal relevance for clinical practice and intervention development, it is time to critically validate the AvT. Here we provide such a formal evaluation against the key criteria proposed for experimental psychopathology (Vervliet & Raes, 2013). Specifically, and in line with recent articles about the validity of US-expectancies (Boddez et al., 2012), exposure procedures (Scheveneels et al., 2016), as well as the *arbitrarily applicable relational responding* on fear and avoidance (Dymond, Bennett, Boyle, Roche, & Schlund, 2017), we assess the *face*, *construct*, *diagnostic*, and *predictive* validity of AvTs. We do that by referring to both human and non-human animal studies. The main message of our article is that although AvTs are extremely useful in providing important theoretical and clinical knowledge about avoidance, further improvement of AvT would strengthen the applicability of the relevant findings to both normal and clinical populations.

## 1. Comparison of AvTs to validity criteria

### 1.1. Face validity

Face validity is generally regarded as the weakest criterion but is commonly the starting point for the development of an experimental model. This criterion refers to how phenomenologically similar is the behavior tested in the used model with the symptoms of the disorder. As we show below, there are at least two reasons AvTs may not meet the criterion of face validity. The first relates to the operationalization of avoidance in humans AvT as simple button presses. The second relates to the nature of the CS; although typically exteroceptive stimuli are used (e.g., pictures, sounds), such stimuli do not apply to disorders in which interoceptive stimuli are avoided (e.g., increased heart rate in panic disorder).

#### 1.1.1. AvTs often operationalize avoidance as simple button presses

In animal AvT studies, avoidance is usually operationalized as

moving away from a dangerous place (e.g., a chamber in which the floor is electrocuted after the presentation of a sound CS) to a safe place (e.g., a chamber where the US is not administrated; Solomon & Wynne, 1953). This type of experimenter-defined response (i.e. overt movements) is phenomenologically similar to also avoidance reactions seen in anxiety disorders (e.g., when a socially anxious person will leave a room that gets crowed). In human studies, however, avoidance is operationalized typically as simple computer button presses (see above). Arguably a computer button press is not phenomenologically similar to, for example, the avoidance of physical activities commonly found in panic disorder, or shuttling, as seen in animal AvTs.

An additional problem with defining avoidance as plain button presses is that the responses are essentially dichotomous (avoid or not avoid). However, avoidance exists in grades from subtle to excessive avoidance. A way to better account for this gradient of responses would be by using continuous, rather than dichotomous, responses. For example, avoidance could be measured as movements of a computer mouse, which allows the continuous registration of the mouse coordinates (e.g., Pittig & Scherbaum, 2018), or via the performance of multiple key presses during the CS presentation (Flores, López, Vervliet, & Cobos, 2018). Alternatively, reaction time tasks could be used (e.g., approach-avoidance tasks; Krypotos et al., 2014; Krypotos, Arnaudova, et al., 2015).

An experimental paradigm that better maps realistic avoidance was used by Glotzbach, Ewald, Andreatta, Pauli, and Mühlberger (2012) (see Grillon, Baas, Cornwell, & Johnson, 2006, for a similar study). Individuals navigated through different virtual contexts using a joystick, with one of the contexts being associated with the presence of an electric stimulus. Then, during a test phase, participants were allowed to choose which environment they could enter. By not entering the fear context, passive avoidance was modeled, at least as a predictor of a contextual CS. Similar procedures could be used also for modeling active avoidance. To illustrate, an individual could be asked to move into a room and then a visual stimulus could be presented (e.g., a different colored light turns on). Some of these stimuli (e.g., a purple light) could operate as predictors of a shock, and as such individuals should exit the room in order to avoid the shock, whereas others (e.g., a blue light) could predict shock absence, meaning that the individual could remain in the room.

#### 1.1.2. The inclusion of costs in AvTs

As explained above, in AvTs the avoidance response is associated with US absence. It could be argued that participants do not have anything to lose by emitting the experimenter-defined action as this action is largely effortless and will lead to the US omission, if a US is scheduled to appear. Yet, in pathological situations, avoidance often relates to the loss of rewarding stimuli (e.g., socializing). A phenomenological valid version of AvTs would include such costs in the standard procedure.

Pointers towards this direction could be given by approach-avoidance conflict tasks (Kirlic, Young, & Aupperle, 2017). To illustrate, Pittig, Brand, Pawlikowski, and Alpers (2014) and Pittig, Schulz, Craske, and Alpers (2014) adapted the Iowa gambling tasks, in which participants chose cards from different decks that include conditional stimuli. Of importance, by not choosing a deck that has higher chances of including CS cards participants lose points, and as such the avoidance response is paired with costs. The role of costs has also been addressed in the conditioning pain literature (e.g., Claes, Karos, Meulders, Crombez, & Vlaeyen, 2014). A recent example is the study by Meulders, Franssen, Fonteyne, and Vlaeyen (2016). It included costs in the avoidance task in terms of how much effort participants should place for moving a robotic arm, with more effort being linked to lower chances of receiving a US. Only a few studies so far have included costs in avoidance learning tasks and they seem to provide, at least in face value, a better model of real-life maladaptive avoidance.

In such experiments, including the same costs across individuals may not be enough. To illustrate, for some participants 'points in a card game' may be important and create a true goal-conflict (approach points vs. avoid shock), but for others this manipulation may not represent a 'true cost'. In parallel, a person with flight phobia may experience costs from not flying only if she enjoys traveling in the first place. In this line, experiments that employ costs could best set individually the costs of the avoidance response.

#### 1.1.3. AvTs include CSs and USs that are fundamentally different from stimuli in real situations

Another challenge related to the avoided stimulus is that studies typically use only exteroceptive stimuli (e.g., pictures, sounds) as CSs. However, individuals often tend to avoid interoceptive stimuli as well. Returning to the social anxiety example, embarrassment can be evoked by the social situation (e.g., negative or neutral attention from others; Colonnesi, Engelhard, & Bögels, 2010), which constitutes an exteroceptive stimulus, or by interoceptive stimuli, such as blushing (Bögels et al., 2010). Recent experiments have introduced new conditioning tasks for testing interoceptive conditioning in humans (Pappens et al., 2013; Zaman et al., 2015), a line of research that is also relevant for pain disorders (Meulders et al., 2016; Meulders, Vansteenwegen, & Vlaeyen, 2011), and suggest that there are differences in conditioning when an interoceptive or exteroceptive stimulus is used as the CS (Peuter, Diest, Vansteenwegen, Bergh, & Vlaeyen, 2011). Similar to the use of interoceptive CSs, interoceptive USs could be used (e.g., $CO_2$ inhalation to induce hyperventilation and panic attack symptoms; Poma et al., 2005). Although the theoretical differences between exteroceptive and interoceptive conditioning has long been debated (Bouton, Mineka, & Barlow, 2001; Razran, 1961), using interoceptive stimuli when studying the acquisition of avoidance of disorders such as panic disorder will improve AvTs in terms of face validity.

In avoidance learning experiments, a shock US is typically used that is adjusted to a level that is definitively unpleasant, but not painful. Although such a stimulus is in line with the guidelines of many ethic committees, such a brief stimulus, that often habituates quickly, is largely different from real-life threat. Although imagery procedures could be used in this regard, where the individual imagines an unpleasant event or personal experience, still the functional similarity between the type of stimuli used in the lab and realistic situations differ fundamentally.

All in all, AvT could be more phenomenologically similar to how avoidance is acquired in real life settings if the task included virtual environments, costs were incorporated, and interoceptive, and not only exteroceptive, CSs were used. Even with these extensions though, fitting the face validity criterion would not ensure that the AvT outcomes could be generalizable outside the lab. For that, we continue by accessing the construct validity of the AvT.

### 1.2. Construct validity

Construct validity refers to how well the experimental paradigm taps into the underlying theory (Nestler & Hyman, 2010; Vervliet & Raes, 2013). Multiple theoretical accounts have been proposed regarding avoidance acquisition (see Krypotos, Effting, Kindt, & Beckers, 2015 for a review). Despite their differences, most theories agree that avoidance is acquired in a two-step procedure, where the individual first acquires fear towards a CS via Pavlovian learning and then learns to avoid the US via instrumental learning (see above). Nonetheless, there has been a long debate as to whether the performed response (shuttling, button-press) denotes avoidance per se, or the closely related, and often phenomenologically similar, *escape* behavior (Sege, Bradley, & Lang, 2018).

Specifically, according to the dual-factor theory (Mowrer, 1951; Mowrer & Lamoreaux, 1942), when a dog shuttles after hearing a tone CS, the dog is escaping the CS, with the US-avoidance being just a by-

**Table 1**
Glossary of actions involved in AvT.

| Term | Definition |
|---|---|
| CS-avoidance | Action that prevents the CS presentation |
| CS-escape | Action that terminates the CS presentation |
| US-avoidance | Action that prevents the presentation of the US |
| US-escape | Action that terminates the US presentation |

effect of the performed response. Such an explanation followed drive-reduction theories at the time, which rejected that a cause of a behavior is a future event (in this case the US presentation). This theory was challenged by findings that show that even when the CS continues after the performance of the avoidance response, which is typical in human AvTs, then avoidance can still be acquired as long as no US is presented (Bolles, Stokes, & Younger, 1966). Mowrer (1960) explained this finding by arguing that even though the avoidance response may not be *directly* followed by the *immediate termination* of the CS, gratification from the CS termination will still occur once the CS presentation ends. Still, the current consensus is that it is the US omission that reinforces the avoidance response (Lovibond, 2006).

The difference between avoidance and escape is also relevant in clinical settings. Let us consider, for example, the case of someone who is afraid that flying will lead to a panic attack. The person could avoid both the CS and the (predicted) US by choosing not to board any plane ever again. Alternatively, this person may choose to encounter the CS, by boarding the plane, but performing *safety behaviors* that will prevent the US from occurring, such as taking anxiolytics. In this case, there is no *CS-escape* or *CS-avoidance* but only *US-avoidance* (see Table 1 for the relevant definitions). These examples show that due to phenomenological similarities, it is often hard to distinguish between CS escape and US avoidance behavior.

There are different ways to modify AvTs to disentangle escape from avoidance responding. To illustrate, CS escape can be disengaged from CS avoidance by intermixing CS-escape trials, in which the operant response during the CS presentation will terminate the CS and prevent the anticipated US, with CS-avoidance trials, in which participants have to respond to a stimulus predicting the CS (e.g., in sequential procedures where a first CS1 predicts a secondly CS2 which subsequently predicts a US; Levis, 1981) so as to prevent the US presentation. Similarly, US-avoidance can be achieved by the cancellation of the US if the operant response is performed during the CS, and US-escape with the termination of the US if the operant response is performed during the US presentation. Note that for the latter to happen, US duration should be long enough to allow the performance of the experimenter-defined response. This is typically not the case: many avoidance-learning procedures use only short USs (e.g., 50msec shocks).

Another way to test the construct validity of the AvT is to blend trials in which avoidance results to the CS termination, with trials in which avoidance *does* not terminate the CS. If the former type of trials would result in avoidance's acquisition, this would suggest that the CS termination could operate as avoidance's reinforcement. If the latter type of trials would also lead to the acquisition of avoidance, this would indicate it is the US cancellation that reinforces avoidance and not CS termination. The above two types of trials could be easily incorporated in a virtual reality experiment where participants would choose between a context in which avoidance would terminate the CS, an another context where avoidance does not result in CS termination.

To recapitulate, the AvT can meet the construct validity criterion if a better distinction is made between the measurements of avoidance and escape behavior.

### 1.3. Predictive validity

Predictive validity refers to the ability of the experimental model to predict performance in disorder-relevant situations. Similar to Scheveneels et al. (2016), we will access this criterion based on two issues: whether AvTs can be used to distinguish individual differences in avoidance acquisition at realistic settings, and whether well-known manipulations (e.g., extinction and response prevention) in the lab that modify avoidance result in behavioral changes when similar procedures (e.g., exposure with response prevention; Abramowitz, 1996; Whittal, Thordarson, & McLean, 2005) are used in the clinic.

#### 1.3.1. AvTs do not account sufficiently for individual fluctuations

Following a traumatic event, not all individuals will develop an anxiety or trauma-related disorder (e.g., PTSD; Engelhard et al., 2007). Likewise, conditioning procedures do not result in similar fear responses and threat expression across all participants (Duits et al., in preparation; Galatzer-Levy, Bonanno, Bush, & LeDoux, 2013; Galatzer-Levy et al., 2014). If AvT serves as a valid laboratory model for the acquisition and maintenance of maladaptive avoidance, it should be sensitive to measure the divergence in the acquisition of maladaptive avoidance. However, most study results rely on group patterns where individual fluctuations are regarded as statistical noise (Lonsdorf & Merz, 2017), an approach that leaves little room for the investigation of individual differences.

To amend the non-consideration of individual differences, different CS types could be used. It has been argued that individual differences in conditioning that are relevant for anxiety-related disorders tend to emerge in case of *weak* instead of *strong* situations (Beckers, Krypotos, Boddez, Effting, & Kindt, 2013; Boddez, Baeyens, Hermans, & Beckers, 2014; Lissek, Pine, & Grillon, 2006). A strong situation would include a warning stimulus that is reliably associated with a specific (threat) outcome, whereas in a weak situation the association between the stimulus and the corresponding outcome is ambiguous (Xia, Dymond, Lloyd, & Vervliet, 2017).

An ambiguous stimulus that gives room for testing individual differences in avoidance conditioning is a generalization stimulus (Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015). In generalization paradigms, participants learn to associate the extremes of a continuum (e.g., a small or a big circle) with the presence or the absence of a shock. Fear responses are then tested across the continuum. Participants typically show a generalization gradient, in which they exhibit elevated responses towards the stimuli closer to the CS that has been previously paired with the US, even though those stimuli were never presented before. Lommen, Engelhard, and van den Hout (2010) used a similar method for testing whether the generalization effect would also lead to differences in avoidance responses. Importantly, they found stronger avoidance in individuals with higher, compared to lower, neuroticism scores (see Arnaudova, Krypotos, Effting, Kindt, & Beckers, 2016 for a partial replication). In similar lines, Hunt, Cooper, Hartnell, and Lissek (2017) and van Meurs, Wiggert, Wicker, and Lissek (2014) showed that individual differences in *distress endurance* and *distraction/suppression* predict the rate of instrumental responding after Pavlovian generalization. Lastly, Vervliet and Indekeu (2015) showed that trait anxiety correlated positively with the levels of responding towards a CS that was not associated with a US (*safe CS*), as well as the decrease rate from the end of an instrumental phase to the end of a test phase, after extinction training.

There are simpler ways to create ambiguous situations. To illustrate, partial reinforcement of avoidance response generates variability in avoidance behavior (e.g., Xia et al., 2017). It would be interesting to test individual differences in such partial reinforcement schedules, especially when costs are involved (see above). For example, studies could test whether individuals high in neuroticism (as in Lommen et al., 2010) or other vulnerability traits (e.g., trait anxiety) may use a 'better safe than sorry' strategy, whereas sensation-seekers may gamble not to do the effortful avoidance behavior. Collectively, it seems that more ambiguous situations leave more room for the study of individual differences in AvTs.

Individual differences in AvTs could also be addressed on an analytic level by using modern statistical techniques, such as latent growth curve modeling (LCGM). LCGM is used to detect heterogeneous subgroups of participants within the entire tested sample. This data-driven procedure has allowed the detection of heterogeneous learning patterns in PTSD (Blessing et al., 2017) and in avoidance training in animals Galatzer-Levy et al. (2014), which was not possible when these animal data were analyzed with group means (Moscarello & LeDoux, 2013).

Specifically, although the original study showed that the whole sample acquired avoidance on average, the re-analyses of the data showed that the animals could be separated into four distinct groups: animals who learn to avoid rapidly, animals who have an average rate of avoidance learning, animals who learn slowly, and animals that did not learn to avoid at all. We have recently replicated these results by using another independent rat sample (Krypotos, Moscarello, Sears, LeDoux, & Galatzer-Levy, 2018). A more extensive use of such statistical models in human data seems fit for testing for individual differences in AvT, and accordingly ensuring the AvT meets the predictive validity criterion.

#### 1.3.2. AvTs for the study of avoidance's reduction

There is currently an increased interest in studying avoidance reduction in the lab (Krypotos & Engelhard, 2018; Treanor & Barry, 2017; van Uijen et al., 2018; Vervliet et al., 2017; Vervliet & Indekeu, 2015). Apart from potential clinical relevance, avoidance reduction studies could be used for testing the predictive validity of AvTs. This can be done by evaluating whether a laboratory procedure results in comparable effects when tested in treatment and vice versa. Regarding the former, the study of Lovibond, Davis, and O'Flaherty (2000) provided partial evidence in this direction. These researchers found that if participants are allowed to avoid the CS during an extinction procedure (i.e. presentation of the CS without the US during an AvT), participants will continue to perceive the CS as threatening, although the CS is no longer paired with a US. This observation is in line with the preservation of threat beliefs in patients with anxiety-related disorders if they follow exposure treatment without response prevention (e.g., Salkovskis, Clark, & Gelder, 1996). Regarding the latter, only a few studies have included elements of clinical interventions in relevant experimental designs.

For example, several studies (Rattel, Miedl, Blechert, & Wilhelm, 2016; Vervliet et al., 2017; Vervliet & Indekeu, 2015) included an extinction phase after an AvT, in which participants encountered the CSs without being able to perform an avoidance response. The results suggest that once the avoidance response becomes available again, participants exhibit high avoidance rates. Regarding animal studies, Solomon, Kamin, and Wynne (1953) trained dogs to shuttle from one side of a box to another, whenever a buzzer would sound, in order to avoid a shock. Then, the experimenters placed a barrier in the middle of the box, something that prevented avoidance, while the buzzer was presented without shock administration. After lowering the barrier, the dogs would start shuttling again whenever the buzzer would sound.

Similarly, Rodriguez-Romaguera, Greenberg, Rasmussen, and Quirk (2016) trained rats to access a platform in order to avoid a shock. In the following phase, a barrier was placed before the platform so that rats could not access it. In the test phase, the barrier was removed and the rats were once again able to access the platform. Most rats showed reduced avoidance but some rats showed failure to extinguish the avoidance response.

Although the above studies are useful for testing avoidance's reduction, it should be noted that exposure therapy entails more, such as cognitive restructuring techniques and behavioral experiments, than just encountering the fear stimulus without a negative outcome (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Scheveneels et al., 2016). As such, more research in needed in order to test whether other aspects of exposure therapy could be enhanced in order to effectively reduce avoidance.

The design of future studies could be informed by the recent work of Treanor and Barry (2017). They argue that avoidance behavior during a CS could operate as conditional inhibitor (a stimulus that is not followed by a US). As such, participants in a conditioning experiment may perform the avoidance response whenever it is available because this response predicts the US absence. The authors propose ways to extinguish conditioned responses to the conditioned inhibitor, such as using USs with different intensities during the acquisition procedure. In comparison with a schedule where the CS is always reinforced by a US with the same intensity, using USs with different intensities will result in larger discrepancy between the CS presentation and US omission during an extinction with response prevention schedule. Such larger discrepancies are linked to deeper learning (Rescorla & Wagner, 1972). Alternatively, similar effects could arise by increasing the CS salience during an extinction with response prevention procedure (e.g., via instructions). This could result in participants being more surprised when the CS is not followed by a US during extinction, resulting in deeper extinction learning again.

#### 1.3.3. AvTs and anxiolytics

Another way to validate the AvTs is by testing whether medication influences the acquisition and/or reduction of conditioned avoidance. Such research is found typically in animals, but with inconclusive results. In an early review of the effects of anxiolytics in conditioned avoidance, Treit (1985) refers to various studies that showed that anxiolytic agents increase, decrease, or have little effect on conditioned avoidance (see also Fernández-Teruel et al., 1991). More recently LeDoux and Pine (2016) mention that anxiolytic drugs that are often used in therapy are based on animal studies showing reduced avoidance in the lab, but, in humans, these drugs only seem to reduce fear and anxiety. Importantly, this fear and anxiety is what often makes individuals seek help (see also Griebel & Holmes, 2013 for an extensive review on anxiolytic drug discovery). As noted by LeDoux and Pine (2016), these results could mean that defensive responses (i.e., avoidance) and fear refer to different brain circuits. All in all, it is unclear whether a specific anxiolytic drug could directly and exclusively reduce avoidance or a specific conditioned fear response. As such it remains to be seen if anxiolytic research would be helpful for testing the predictive validity of AvTs.

Summarizing the previous points, AvT can better meet the predictive validity criterion if individual differences are addressed by either the use of weaker situations and/or employment of modern statistical procedures. Lastly, it could prove useful to further test additional procedures of avoidance's reduction, a goal of tremendous clinical relevance.

### 1.4. Diagnostic validity

Diagnostic validity refers to the ability of the experimental model to distinguish between at-risk individuals and healthy individuals (Boddez et al., 2012; Vervliet & Raes, 2013). The importance of this criterion lays in demonstrating that the tested model addresses processes that are only found in patient populations (Vervliet & Raes, 2013). There are different ways to support the diagnostic validity.

In psychology, typically self-report questionnaires are used for discriminating, for example, individuals with low and high anxiety (e.g., STAI Spielberger, Gorsuch, & Lushene, 1970).

Accordingly, AvTs would meet the criterion of diagnostic validity if they would detect which individuals have higher chances of exhibiting excessive avoidance, for instance in the aftermath of major stress (e.g., a serious car accident). A cross-sectional study could also be carried out to detect differences in performance between clinical and healthy individuals (as in Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007). Lastly, the AvT could be used for detecting relevant biomarkers that could predict the development of avoidance symptomatology. In a recent review Lonsdorf and Kalisch (2011) provided evidence that,

among others, low levels in the serotonin transporter were related to stronger, and possibly more persistent, fear learning, and to the development of PTSD symptomatology. It would be useful if human and animal studies explored the potential role of specific biomarkers in the acquisition and reduction of avoidance.

To date, and despite the plethora of ways in which this could be addressed, there are no published studies that provide evidence for or against this criterion of validity. This is quite astonishing given the central role of avoidance conditioning in psychological theories of clinical anxiety. Studies that test the diagnostic validity of AvTs are timely.

## 2. Conclusion

There is currently a surge of interest in the experimental study of human avoidance (Krypotos, Effting, et al., 2015; LeDoux et al., 2017). By using AvTs, experimental psychologists often strive to gain knowledge on the acquisition and extinction of (mal)adaptive avoidance.

Although currently used also for determining the cognitive mechanisms of avoidance's acquisition and reduction, a formal validation of whether AvTs fit these purposes was lacking. As we have shown above, AvTs often fall short in terms of face, construct, and predictive validity when it refers to maladaptive avoidance, or when human AvTs are compared to the corresponding animal AvTs. Based on examples from the avoidance learning literature we have argued that given these limitations, the generalization of AvTs findings to clinical populations, and of animal to human studies, may be limited. In this line, we have made some concrete suggestions regarding the revisions of AvTs so that they better meet the tested validity criteria. Among others we have suggested the adoption of virtual reality procedures, use of interoceptive stimuli, and the investigation of more procedures that may lead to avoidance's reduction. Although further suggestions could be included, the main point of our article is that the further extension of the AvT is important if this model is to be used for testing maladaptive avoidance behavior.

We conclude that despite the important contributions of human avoidance literature in understanding avoidance learning, firmer conclusions relating to how maladaptive avoidance is acquired would be reached by using more valid AvTs. We hope that by following the suggestions mentioned above, the validity of AvTs will increase, something that could result in richer theoretical and clinical insights.

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## References

Abramowitz, J. S. (1996). Variants of exposure and response prevention in the treatment of obsessive-compulsive disorder: A meta-analysis. *Behavior Therapy, 27*, 583–600.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders: DSM 5*. Arlington, VA: American Psychiatric Publishing.

Arnaudova, I., Krypotos, A.-M., Effting, M., Kindt, M., & Beckers, T. (2016). Fearing shades of grey: Individual differences in fear responding towards generalisation stimuli. *Cognition & Emotion,* 1–16.

Beckers, T., & Craske, M. G. (2017). Avoidance and decision making in anxiety: An introduction to the special issue. *Behaviour Research and Therapy, 96*, 1–2.

Beckers, T., Krypotos, A.-M., Boddez, Y., Effting, M., & Kindt, M. (2013). What's wrong with fear conditioning? *Biological Psychology, 92*, 90–96.

Blessing, E. M., Reus, V., Mellon, S. H., Wolkowitz, O. M., Flory, J. D., Bierer, L., ... Marmar, C. R. (2017). Biological predictors of insulin resistance associated with posttraumatic stress disorder in young military veterans. *Psychoneuroendocrinology, 82*, 91–97.

Boddez, Y., Baeyens, F., Hermans, D., & Beckers, T. (2014). A learning theory approach to anxiety disorders: Human fear conditioning and the added value of complex acquisition procedures. In P. Emmelkamp, & T. Ehring (Eds.). *The Wiley handbook of anxiety disorders. Volume 1: Theory & research*(pp. 85–103). Sussex, UK: John Wiley & Sons.

Boddez, Y., Vervliet, B., Baeyens, F., Lauwers, S., Hermans, D., & Beckers, T. (2012). Expectancy bias in a selective conditioning procedure: Trait anxiety increases the threat value of a blocked stimulus. *Journal of Behavior Therapy and Experimental Psychiatry, 43*, 832–837.

Bögels, S. M., Alden, L., Beidel, D. C., Clark, L. A., Pine, D. S., Stein, M. B., et al. (2010). Social anxiety disorder: Questions and answers for the DSM-V. *Depression and Anxiety, 27*, 168–189.

Bolles, R. C., Stokes, L. W., & Younger, M. S. (1966). Does CS termination reinforce avoidance behavior? *Journal of Comparative & Physiological Psychology, 62*, 201–207.

Bouton, M. E. (2000). A learning theory perspective on lapse, relapse, and the maintenance of behavior change. *Health Psychology, 19*, 57–63.

Bouton, M. E., Mineka, S., & Barlow, D. H. (2001). A modern learning theory perspective on the etiology of panic disorder. *Psychological Review, 108*, 4–32.

Claes, N., Karos, K., Meulders, A., Crombez, G., & Vlaeyen, J. W. (2014). Competing goals attenuate avoidance behavior in the context of pain. *The Journal of Pain, 15*, 1120–1129.

Colonnesi, C., Engelhard, I. M., & Bögels, S. M. (2010). Development in children's attribution of embarrassment and the relationship with theory of mind and shyness. *Cognition & Emotion, 24*, 514–521.

Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T., & Vervliet, B. (2014). Maximizing exposure therapy: An inhibitory learning approach. *Behaviour Research and Therapy, 58*, 10–23.

Duits, P., Baas, J. M. P., Engelhard, I. M., Richter, J., van Dijk H. M., H., Limberg, A., …. Cath, D. C. (in preparation). Latent fear conditionign trajectories in anxiety disorders and their predictive value on treatment outcomes.

Dymond, S., Bennett, M., Boyle, S., Roche, B., & Schlund, M. (2017). Related to anxiety: Arbitrarily applicable relational responding and experimental psychopathology research on fear and avoidance. *Perspectives on Behavior Science,* 1–25.

Dymond, S., Dunsmoor, J. E., Vervliet, B., Roche, B., & Hermans, D. (2015). Fear generalization in humans: Systematic review and implications for anxiety disorder research. *Behavior Therapy, 46*, 561–582.

Dymond, S., Roche, B., Forsyth, J. P., Whelan, R., & Rhoden, J. (2007). Transformation of avoidance response functions in accordance with same and opposite relational frames. *Journal of the Experimental Analysis of Behavior, 88*, 249–262.

Dymond, S., Roche, B., Forsyth, J. P., Whelan, R., & Rhoden, J. (2008). Derived avoidance learning: Transformation of avoidance response functions in accordance with same and opposite relational frames. *Psychological Record, 58*, 269–286.

Engelhard, I. M., Van Den Hout, M. A., Weerts, J., Arntz, A., Hox, J. J. C. M., & McNally, R. J. (2007). Deployment-related stress and trauma in Dutch soldiers returning from Iraq. *British Journal of Psychiatry, 191*, 140–145.

Fernández-Teruel, A., Escorihuela, R., Nunez, J., Zapata, A., Boix, F., Salazar, W., et al. (1991). The early acquisition of two-way (shuttle-box) avoidance as an anxiety-mediated behavior: Psychopharmacological validation. *Brain Research Bulletin, 26*, 173–176.

Flores, A., López, F. J., Vervliet, B., & Cobos, P. L. (2018). Intolerance of uncertainty as a vulnerability factor for excessive and inflexible avoidance behavior. *Behaviour Research and Therapy, 104*, 34–43.

Galatzer-Levy, I. R., Bonanno, G. A., Bush, D. E., & LeDoux, J. E. (2013). Heterogeneity in threat extinction learning: Substantive and methodological considerations for identifying individual difference in response to stress. *Frontiers in Behavioral Neuroscience, 7*.

Galatzer-Levy, I. R., Moscarello, J., Blessing, E. M., Klein, J., Cain, C. K., & LeDoux, J. E. (2014). Heterogeneity in signaled active avoidance learning: Substantive and methodological relevance of diversity in instrumental defensive responses to threat cues. *Frontiers in Systems Neuroscience, 8*.

Glotzbach, E., Ewald, H., Andreatta, M., Pauli, P., & Mühlberger, A. (2012). Contextual fear conditioning predicts subsequent avoidance behaviour in a virtual reality environment. *Cognition & Emotion, 26*, 1256–1272.

Griebel, G., & Holmes, A. (2013). 50 years of hurdles and hope in anxiolytic drug discovery. *Nature Reviews Drug Discovery, 12*, 667–687.

Grillon, C., Baas, J. M., Cornwell, B., & Johnson, L. (2006). Context conditioning and behavioral avoidance in a virtual reality environment: Effect of predictability. *Biological Psychiatry, 60*, 752–759.

Hofmann, S. G., & Hay, A. C. (2018). Rethinking avoidance: Toward a balanced approach to avoidance in treating anxiety disorders (in press) *Journal of Anxiety Disorders*.

Hunt, C., Cooper, S. E., Hartnell, M. P., & Lissek, S. (2017). Distraction/suppression and distress endurance diminish the extent to which generalized conditioned fear is associated with maladaptive behavioral avoidance. *Behaviour Research and Therapy, 96*, 90–105.

Kirlic, N., Young, J., & Aupperle, R. L. (2017). Animal to human translational paradigms relevant for approach avoidance conflict decision making. *Behaviour Research and Therapy, 96*, 14–29.

Krypotos, A.-M., Arnaudova, I., Effting, M., Kindt, M., & Beckers, T. (2015). Effects of approach-avoidance training on the extinction and return of fear responses. *PloS One, 10*, e0131581.

Krypotos, A.-M., Effting, M., Arnaudova, I., Kindt, M., & Beckers, T. (2014). Avoided by association acquisition, extinction, and renewal of avoidance tendencies toward conditioned fear stimuli. *Clinical Psychological Science, 2*, 336–343.

Krypotos, A.-M., Effting, M., Kindt, M., & Beckers, T. (2015). Avoidance learning: A review of theoretical models and recent developments. *Frontiers in Behavioral*

*Neuroscience, 9*.
Krypotos, A.-M., & Engelhard, I. M. (2018). Testing a novelty-based extinction procedure for the reduction of conditioned avoidance. *Journal of Behavior Therapy and Experimental Psychiatry, 60*, 22–28.
Krypotos, A.-M., Moscarello, J. M., Sears, R. M., LeDoux, E., Joseph, & Galatzer-Levy, I. (2018). A principled method to identify individual differences and behavioral shifts in signaled active avoidance (in press) *Learning & Memory*.
LeDoux, J. E., Moscarello, J., Sears, R., & Campese, V. (2017). The birth, death and resurrection of avoidance: A reconceptualization of a troubled paradigm. *Molecular Psychiatry, 22*, 24–36.
LeDoux, J. E., & Pine, D. S. (2016). Using neuroscience to help understand fear and anxiety: A two-system framework. *American Journal of Psychiatry, 173*, 1083–1093.
Levis, D. J. (1981). Extrapolation of two-factor learning theory of infrahuman avoidance behavior to psychopathology. *Neuroscience & Biobehavioral Reviews, 5*, 355–370.
Lissek, S., Pine, D. S., & Grillon, C. (2006). The 'strong situation': A potential impediment to studying the psychobiology and pharmacology of anxiety disorders. *Biological Psychology, 72*, 265–270.
Lommen, M. J., Engelhard, I. M., & van den Hout, M. A. (2010). Neuroticism and avoidance of ambiguous stimuli: Better safe than sorry? *Personality and Individual Differences, 49*, 1001–1006.
Lonsdorf, T. B., & Kalisch, R. (2011). A review on experimental and clinical genetic associations studies on fear conditioning, extinction and cognitive-behavioral treatment. *Translational Psychiatry, 1*, e41.
Lonsdorf, T. B., & Merz, C. J. (2017). More than just noise: Inter-individual differences in fear acquisition, extinction and return of fear in humans–biological, experiential, temperamental factors, and methodological pitfalls. *Neuroscience & Biobehavioral Reviews, 80*, 703–728.
Lovibond, P. F. (2006). Fear and avoidance: An integrated expectancy model. In M. G. Craske, D. Hermans, & D. Vansteenwegen (Eds.). *Fear and learning: From basic processes to clinical implications* (pp. 117–132). American Psychological Association.
Lovibond, P. F., Davis, N. R., & O'Flaherty, A. S. (2000). Protection from extinction in human fear conditioning. *Behaviour Research and Therapy, 38*, 967–983.
Lovibond, P. F., Mitchell, C. J., Minard, E., Brady, A., & Menzies, R. G. (2009). Safety behaviours preserve threat beliefs: Protection from extinction of human fear conditioning by an avoidance response. *Behaviour Research and Therapy, 47*, 716–720.
Lovibond, P. F., Saunders, J. C., Weidemann, G., & Mitchell, C. J. (2008). Evidence for expectancy as a mediator of avoidance and anxiety in a laboratory model of human avoidance learning. *The Quarterly Journal of Experimental Psychology, 61*, 1199–1216.
Luyten, L., Vansteenwegen, D., van Kuyck, K., Gabriëls, L., & Nuttin, B. (2011). Contextual conditioning in rats as an animal model for generalized anxiety disorder. *Cognitive, Affective, & Behavioral Neuroscience, 11*, 228–244.
Meulders, A., Franssen, M., Fonteyne, R., & Vlaeyen, J. W. (2016). Acquisition and extinction of operant pain-related avoidance behavior using a 3 degrees-of-freedom robotic arm. *Pain, 157*, 1094–1104.
Meulders, A., Vansteenwegen, D., & Vlaeyen, J. W. (2011). The acquisition of fear of movement-related pain and associative learning: A novel pain-relevant human fear conditioning paradigm. *Pain, 152*, 2460–2469.
van Meurs, B., Wiggert, N., Wicker, I., & Lissek, S. (2014). Maladaptive behavioral consequences of conditioned fear-generalization: A pronounced, yet sparsely studied, feature of anxiety pathology. *Behaviour Research and Therapy, 57*, 29–37.
Michael, T., Blechert, J., Vriends, N., Margraf, J., & Wilhelm, F. H. (2007). Fear conditioning in panic disorder: Enhanced resistance to extinction. *Journal of Abnormal Psychology, 116*, 612.
Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on the etiology of anxiety disorders: it's not what you thought it was. *American Psychologist, 61*, 10–26.
Moscarello, J. M., & LeDoux, J. E. (2013). Active avoidance learning requires prefrontal suppression of amygdala-mediated defensive reactions. *Journal of Neuroscience, 33*, 3815–3823.
Mowrer, O. H. (1951). Two-factor learning theory: Summary and comment. *Psychological Review, 58*, 350–354.
Mowrer, O. H. (1956). Two-factor learning theory reconsidered, with special reference to secondary reinforcement and the concept of habit. *Psychological Review, 63*, 114.
Mowrer, O. H. (1960). *Learning theory and behavior*. New York, US: John Wiley.
Mowrer, O. H., & Lamoreaux, R. R. (1942). Avoidance conditioning and signal duration–a study of secondary motivation and reward. *Psychological Monographs, 54*, 1–34.
Nestler, E. J., & Hyman, S. E. (2010). Animal models of neuropsychiatric disorders. *Nature Neuroscience, 13*, 1161–1169.
Pappens, M., Van den Bergh, O., Vansteenwegen, D., Ceunen, E., De Peuter, S., & Van Diest, I. (2013). Learning to fear obstructed breathing: Comparing interoceptive and exteroceptive cues. *Biological Psychology, 92*, 36–42.
Peuter, S., Diest, I., Vansteenwegen, D., Bergh, O., & Vlaeyen, J. W. (2011). Understanding fear of pain in chronic pain: Interoceptive fear conditioning as a novel approach. *European Journal of Pain, 15*, 889–894.
Pittig, A., Brand, M., Pawlikowski, M., & Alpers, G. W. (2014). The cost of fear: Avoidant decision making in a spider gambling task. *Journal of Anxiety Disorders, 28*, 326–334.
Pittig, A., & Scherbaum, S. (2018). Temporal dynamics of threat avoidance in approach-avoidance conflicts in anxious individuals. *10th European meeting on human fear conditioning*.
Pittig, A., Schulz, A., Craske, M., & Alpers, G. (2014). Acquisition of behavioral avoidance: Task-irrelevant conditioned stimuli trigger costly decisions. *Journal of Abnormal Psychology, 123*, 314–329.
Poma, S. Z., Milleri, S., Squassante, L., Nucci, G., Bani, M., Perini, G. I., et al. (2005). Characterization of a 7% carbon dioxide (CO2) inhalation paradigm to evoke anxiety symptoms in healthy subjects. *Journal of Psychopharmacology, 19*, 494–503.
Rattel, J. A., Miedl, S. F., Blechert, J., & Wilhelm, F. H. (2016). Higher threat avoidance costs reduce avoidance behaviour which in turn promotes fear extinction in humans. *Behaviour Research and Therapy, 96*, 37–46.
Razran, G. (1961). The observable and the inferable conscious in current Soviet psychophysiology: Interoceptive conditioning, semantic conditioning, and the orienting reflex. *Psychological Review, 68*, 81–147.
Rescorla, R. A., & Wagner, A. R. (1972). A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A. H. Black, & W. F. Prokasy (Eds.). *Classical conditioning II: Current research and theory* (pp. 64–99). New York: Appleton-Centrury-Crofts.
Rodriguez-Romaguera, J., Greenberg, B. D., Rasmussen, S. A., & Quirk, G. J. (2016). An avoidance-based of exposure with response prevention therapy for obsessive-compulsive disorder. *Biological Psychiatry, 80*, 534–540.
Salkovskis, P. M., Clark, D. M., & Gelder, M. G. (1996). Cognition-behaviour links in the persistence of panic. *Behaviour Research and Therapy, 34*, 453–458.
Scheveneels, S., Boddez, Y., Vervliet, B., & Hermans, D. (2016). The validity of laboratory-based treatment research: Bridging the gap between fear extinction and exposure treatment. *Behaviour Research and Therapy, 86*, 87–94.
Sege, C. T., Bradley, M. M., & Lang, P. J. (2018). Avoidance and escape: Defensive reactivity and trait anxiety. *Behaviour Research and Therapy, 104*, 62–68.
Servatius, R. J. (2016). Avoidance: From basic science to psychopathology. *Frontiers in Behavioral Neuroscience, 10*.
Solomon, R. L., Kamin, L. J., & Wynne, L. C. (1953). Traumatic avoidance learning: The outcomes of several extinction procedures with dogs. *Journal of Abnormal and Social Psychology, 48*, 291–302.
Solomon, R. L., & Wynne, L. C. (1953). Traumatic avoidance learning: Acquisition in normal dogs. *Psychological Monographs: General and Applied, 67*, 1–19.
Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *Manual for the state-trait anxiety inventory*. Palo Alto, CA: Consulting Psychologists Press.
Treanor, M., & Barry, T. J. (2017). Treatment of avoidance behavior as an adjunct to exposure therapy: Insights from modern learning theory. *Behaviour Research and Therapy, 96*, 30–36.
Treit, D. (1985). Animal models for the study of anti-anxiety agents: A review. *Neuroscience & Biobehavioral Reviews, 9*, 203–222.
van Uijen, S. L., Leer, A., & Engelhard, I. M. (2018). Safety behavior after extinction causes a return of threat expectancies. *Behavior Therapy, 49*, 450–458.
Vervliet, B., & Indekeu, E. (2015). Low-cost avoidance behaviors are resistant to fear extinction in humans. *Frontiers in Behavioral Neuroscience, 9*.
Vervliet, B., Lange, I., & Milad, M. R. (2017). Temporal dynamics of relief in avoidance conditioning and fear extinction: Experimental validation and clinical relevance. *Behaviour Research and Therapy, 96*, 66–78.
Vervliet, B., & Raes, F. (2013). Criteria of validity in experimental psychopathology: Application to models of anxiety and depression. *Psychological Medicine, 43*, 2241–2244.
Whittal, M. L., Thordarson, D. S., & McLean, P. D. (2005). Treatment of obsessive–compulsive disorder: Cognitive behavior therapy vs. exposure and response prevention. *Behaviour Research and Therapy, 43*, 1559–1576.
Xia, W., Dymond, S., Lloyd, K., & Vervliet, B. (2017). Partial reinforcement of avoidance and resistance to extinction in humans. *Behaviour Research and Therapy, 96*, 79–89.
Zaman, J., Weltens, N., Ly, H. G., Struyf, D., Vlaeyen, J., Van den Bergh, O., ... Van Diest, I. (2015). Interoceptive fear learning alters visceral perception. *Psychosomatic Medicine, 78*, 248–258.