



Temporal dynamics of relief in avoidance conditioning and fear extinction: Experimental validation and clinical relevance



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ABSTRACT

The learning principles that guide the acquisition and extinction of avoidance are not fully understood. We developed a novel paradigm to study the temporal dynamics of relief, a putative reinforcer of avoidance, and the recovery of fear and avoidance following extinction. During conditioning, the avoidance action canceled the aversive unconditional stimulus (US), without terminating the predictive conditional stimulus (CS). Relief pleasantness was rated after fixed CS offsets, when US omission occurred. Avoidance was effective to one CS, but not to another, to track stimulus-specific avoidance learning. Fear was extinguished under response prevention in a separate context. Recovery tests took place 24 h later, in both contexts and with a monetary cost added to the avoidance action. We found that avoidance gradually became stimulus-specific during conditioning, but hardly recovered during delayed testing. Across all phases, initial omissions of the aversive US triggered relief that gradually declined over consecutive omissions, in line with a theoretical prediction error signal. Participants that scored low on distress tolerance, however, displayed sustained levels of relief over continuous omissions. We propose that such forms of sustained relief may produce over-reinforcement of foregoing avoidance actions and promote the development of pathological avoidance. The current paradigm represents an efficacious tool to study the temporal dynamics of relief across avoidance learning and fear extinction and to characterize relief dysregulations in relation to psychopathology.

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1. Introduction

Problematic fear and avoidance are two cardinal symptoms that cut across the anxiety disorders, and extend to post-traumatic stress disorder and obsessive-compulsive disorder (American Psychiatric Association, 2013). While fear and its extinction have been the core focus of clinical and pre-clinical anxiety research for decades (see Milad & Quirk, 2012; Vervliet, Craske, & Hermans, 2013; Vervliet, Baeyens, Van den Bergh, & Hermans, 2013), research on avoidance is only starting to catch up. One reason for studying avoidance in its own right is that avoidance is not merely a by-product of fear. Levels of fear and avoidance can co-vary, vary inversely, or vary independently in anxiety patients (Rachman & Hodgson, 1974), and avoidance behaviors often persist in the

absence of any measurable fear reaction in animals (Mineka, 1979). Avoidance behaviors can even survive fear extinction (Bravo-Rivera, Roman-Ortiz, Montesinos-Cartagena, & Quirk, 2015; Vervliet & Indekeu, 2015). Hence, changing avoidance behavior seems to require more than changing fear response alone (see Arnaudova, Kindt, Fanselow, & Beckers, 2017; Treanor & Barry, 2017). Also, the mechanism that pushes adaptive into maladaptive avoidance remains largely unknown. There is a pressing need for human avoidance paradigms that can help identifying mechanistic deficits that underly pathological avoidance in patients with anxiety-related disorders. For that purpose, we tested in healthy individuals a newly developed paradigm to study relief as a putative reinforcer of avoidance and to probe the recovery of fear and avoidance following extinction.

Relief is a positive emotion that is triggered during unexpected omissions of a negative event (Deutsch, Smith, Kordts-Freudinger, & Reichardt, 2015; Vlemincx et al., 2009). Thus, relief can be understood as a 'pleasant surprise', comparable to the sudden receipt

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of a positive reward (Leknes, Lee, Berna, Andersson, & Tracey, 2011). In reinforcement learning algorithms, 'pleasant surprise' is formalized as the valence-signed prediction error (PE), the difference between expected reward and actual reward. It serves as the critical teaching signal for reinforcement learning that promotes repetition of the foregoing action to maximize future rewards (Sutton & Barto, 1998). In the case of relief, the 'pleasant surprise' is formalized as the difference between expected punishment and its actual omission, which reinforces the foregoing avoidance action in order to minimize future punishments (Maia, 2010; Moutoussis, Bentall, Williams, & Dayan, 2008). Specifically, the PE signal is thought to govern the rate of action-safety learning, in which the avoidance action becomes associated with its safety consequences in order to promote selection of this avoidance action during similar motivational states in the future (when safety is desired). Eventually, when the safety consequences are fully anticipated, omissions of punishment no longer trigger 'pleasant surprise' (reward PE). It follows that the PE is assumed to be high during initial avoidance learning instances and to gradually decrease over consecutive avoidance instances (Maia, 2010; Moutoussis et al., 2008).

An unexplored question is how action-safety learning develops in patients with anxiety disorders, and how this impacts the temporal dynamics of the 'pleasant surprise' PE. Laboratory studies have shown that anxiety patients are generally impaired in safety-signal learning, namely, learning which stimuli predict safety (Briscione, Jovanovic, & Norrholm, 2014; Duits et al., 2015). If these impairments generalize to action-safety learning in avoidance, omissions of punishment (i.e., safety) would remain somewhat unexpected and continuously trigger a 'pleasant surprise' PE. We propose that these continuous reinforcements give way to a habitization of the avoidance action, by which it becomes a behavioral routine that is disconnected from current goals and motivational states and is therefore more resistant to change (Gillan et al., 2014). In particular, we hypothesize that impaired learning of the action-safety association produces continuous reinforcements that promote the development of an association between the CS and the action instead. This association does promote repetition of the avoidance action to minimize future punishments, but in an inflexible manner that may develop into the unproductive/unnecessary avoidance behaviors that characterize anxiety disorders. This type of stimulus-response learning may be intact in anxiety patients, as it does not rely on an ability to learn to predict safety. In summary, we propose that safety-learning impairments may push adaptive, goal-directed avoidance into maladaptive, habitual avoidance through a dysregulation of PE signaling.

Current avoidance paradigms are not designed to study the interplay between safety learning and PE signaling in avoidance (but see Eldar, Hauser, Dayan, & Dolan, 2016, for a decision-making study that focused on neural PE signaling in avoidant decision-making). Some avoidance paradigms track emotional learning processes *before* each avoidance action (at CS onsets), which focuses on the role of CS-induced fear and/or expected controllability, but not on avoidance-induced safety or relief (e.g., van Meurs, Wiggert & Lissek; Delgado, Jou, LeDoux, & Phelps, 2009). Other paradigms do not signal the US (e.g., Collins, Mendelsohn, Cain, & Schiller, 2014), use very brief CS presentations (Gillan et al., 2014), or terminate the CS upon avoidance actions (mostly used in animal studies, e.g., Moscarello & LeDoux, 2013). These procedures make it difficult to disentangle avoidance-induced safety from omission-induced relief. Hence, although these paradigms contribute importantly to the study of avoidance, they are not ideally suited for detailed examination of the temporal dynamics of

relief. In addition, most avoidance studies have focused on the conditioning of avoidance *per se*, leaving the extinction and recovery of avoidance behavior relatively unexplored in human research (but see Vervliet & Indekeu, 2015; Schlund, Brewer, Richman, Magee, & Dymond, 2015; Cameron, Schlund, & Dymond, 2015).

The current study tested in healthy individuals a newly developed protocol to track the temporal dynamics of relief and to probe the recovery of fear and avoidance. For that purpose, we integrated an avoidance protocol previously developed by Vervliet and Indekeu (2015) with a well-established fear extinction/recovery paradigm (Milad, Orr, Pitman, & Rauch, 2005), and added subjective ratings of relief pleasantness on a trial-by-trial basis (Leknes et al., 2011). Of note, CS durations were always fixed, irrespective of avoidance actions. This allowed Vervliet and Indekeu (2015) to track action-safety learning, as evidenced by gradual decreases in threat-expectancy and skin conductance reactivity immediately *after* each avoidance action but *before* CS offset. In the novel protocol, we added a relief pleasantness rating scale *after* each CS offset, when US omission occurred (Fig. 1A). We explicitly asked for the *pleasantness* of relief to probe the rewarding experience of 'pleasant surprise' as the valence-signed PE signal that is thought to reinforce avoidance actions (reinforcement learning; Moutoussis et al., 2008). In support, relief pleasantness ratings during unexpected omissions of pain were previously found to correlate with activations in the ventral striatum, a key node of reward prediction error processing (Leknes et al., 2011).

We also added an extra CS to the experimental design (Fig. 1B), in line with the original extinction paradigm (Milad et al., 2005). The avoidance action did not cancel the aversive US to this CS (CS+UU, the *unproductive* CS+, in contrast to CS+EE, the *effective* CS+; see also Schlund et al., 2015). Avoidance actions to a CS- that was never followed by the aversive US were *unnecessary*. This allowed us to track the differential development of effective, unproductive, and unnecessary avoidance actions. In addition, because only CS+EE underwent fear extinction on day 1, CS+UU served as a comparison for extinction tests on day 2 (cf. Milad et al., 2005). Finally, we inserted a context change between avoidance conditioning and fear extinction, and we tested fear, avoidance and relief in both contexts 24 h later. This allowed us to explore the ability of fear extinction to reduce avoidance actions within both the extinction and conditioning context, and to examine the interplay with fear and relief. Of note, a small monetary cost was added to each avoidance action during these tests, in order to explore effects of increased response costs on continued avoidance.

Anxiety- and avoidance-related personality traits have been found to correlate with avoidance frequency in other paradigms (trait anxiety, Vervliet & Indekeu, 2015; neuroticism, Lommen, Engelhard, & van den Hout, 2010; experiential avoidance, van Meurs, Wiggert, Wicker, & Lissek, 2014). In the current study, we wanted to explore individual differences in the regulation of relief. For that purpose, we focused on distress tolerance, a transdiagnostic risk factor that represents one's ability to experience and endure negative emotional states (Simons & Gaher, 2005) and that is associated with a broad range of anxiety symptomatology independent of general negative affect (Keough, Riccardi, Timpano, Mitchell, & Schmidt, 2010). Because individuals with lower levels of distress tolerance may find anticipation and endurance of the aversive US more taxing, we hypothesized that these individuals would experience more relief in reaction to US omissions. To the extent that relief pleasantness reinforces avoidance, lower tolerance of distress would also spur increased engagement in avoidance actions.

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