



A behavioural neuroscience perspective on the aetiology and treatment of anxiety disorders



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ABSTRACT

Over the past decades, behaviour and cognitive psychology have produced fruitful and mutually converging theories from which hypotheses could be derived on the nature and origin of fear and anxiety disorders. Notwithstanding the emergence of effective treatments, there are still many questions that remain to be answered. Here, I will argue that the burgeoning field of behavioural neuroscience may advance our understanding of fear, anxiety disorders and its treatments. Decades of fear-conditioning research across species have begun to elucidate the neurobiological mechanisms underlying associative fear learning and memory. The fear-conditioning paradigm provides a well-controlled and fine-grained research platform to examine these processes. Although the traditional fear conditioning paradigm was originally designed to unveil general principles of fear (un)learning, it is well-suited to understand the transition from normal fear to pathological fear and the mechanisms of change. This paper presents 1) a selection of fear conditioning studies on the generalization and persistence of associative fear memory as intermediate phenotypes of fear and anxiety disorders, and 2) insights from neuroscience on the malleability of fear memory with the potential to provide a long-term cure for anxiety and related disorders.

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Our brains are programmed to learn. For most animals their brains are largely encoded by their genes, whereas human beings have more behaviour that is learned and relatively less is programmed right from the beginning (Roberts, 2014). Although fear is innately programmed, and is well conserved across species, we still have to learn about the potential dangers in life, and even more important about the predictors of danger. Given that associative fear memory lies at the root of fear and anxiety disorders, there has been considerable interest in understanding neurobiological mechanisms that mediate long-term storage and retrieval of fear memories, as well as the mechanisms underlying the weakening of these memories. The quintessential model to study associative fear memory is Pavlovian fear conditioning (Barlow, 2002; LeDoux, 2000; Mineka & Zinbarg, 2006; Phelps & LeDoux, 2005). A clear advantage of this paradigm is that it is well-suited for research across species (e.g., rats, crabs, primates and humans) to probe the neural, cellular and molecular mechanisms underlying associative

fear learning and memory. However, the problem in anxiety disorders is not the fear memory itself – programmed throughout evolution to be rapidly acquired – but the persistence and the broader generalization of fear to familiar and novel stimuli and contexts in the absence of actual danger. In this review I will discuss how insights from behavioural neuroscience on fear conditioning may contribute to a better understanding of the transition from normal to abnormal fear. Furthermore, I will argue that insights into the plasticity of fear memory might eventually advance treatments for pathological anxiety. In the past century, the behavioural and cognitive theories were of great value for the development of effective interventions for fear and anxiety disorders. Yet new insights from the behavioural neuroscience may eventually enrich the field.

Experimental research on fear and anxiety disorders

The empirical science of fear and anxiety disorders harks back to the introduction of behaviourism in the fifties. The idea that stimuli could control behaviour strongly advanced the science of fear and anxiety because it enabled to deduce hypotheses that could be critically tested by observations. Thus, instead of being dependent

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on participants' introspective capabilities, reliable and accurate methods of behavioural assessment became the standard. One of the highlights was evidently the development of behaviour therapy, which was grounded on the notion that if fear learning lies at the heart of anxiety disorders, it should also be possible to unlearn fear. Over the years, numerous variants of behaviour therapy for fear and anxiety disorders have been evolved and tested. Of these therapies exposure to the threatening cue is still considered one of the most effective ingredients of successful treatment (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014).

A shortcoming of the early behavioural paradigm was that it eschewed the mental processes. This opened avenues for the cognitive revolution and the information-processing paradigm in the late seventies. Stimulus–response associations were no longer a central topic of interest in clinical psychology and were replaced by processes of attention, memory, interpretation, attribution and representation (Williams, Watts, MacLeod, & Mathews, 1988). The cognitive theory on psychopathology postulated that disorder specific memory representations influence lower level cognitive processes resulting in processing biases for concern-related information. From the eighties onwards, the information processing paradigm has dominated the field with (1) Beck (1967) and Ellis (1958) as the founding fathers of cognitive therapy; (2) the seminal work of Lang (1977, 1979) followed by the highly influential work of Edna Foa and Michael Kozak on fear representation (1986); and (3) the development of experimental procedures by Mathews and MacLeod (1985) that enabled to objectively test the information processing biases. In the eighties and nineties, behaviour theory was supposed to be virtually irrelevant for our understanding of anxiety disorders and the development of better treatments, but the paradigm never really lost ground in the neuroscience of fear memory.

Currently, cognitive behavioural treatment (CBT) for anxiety and related disorders dominates clinical practice with a combination of intervention techniques inferred from both the behavioural and cognitive theory (Hofmann & Smits, 2008). It evolved from a long tradition of experimental research aimed to unveil disorder-specific processes underlying the aetiology and maintenance of that particular disorder. Parallel to this disorder-specific model, transdiagnostic cognitive and behavioural processes (i.e., information processing biases, ruminations) have been recognized as potential factors to target in treatment (Hallion & Ruscio, 2011; Harvey, Watkins, Mansell, & Shafran, 2004). Even though CBT is considered to be the most effective treatment for anxiety and related disorders, it is still far from optimal (Craske et al., 2014; Hofmann & Smits, 2008). There are many patients who fail to benefit from CBT, or fail to maintain their gains. The current information-processing theories do not satisfactorily explain why treatment sometimes fails. In fact, there is relatively little knowledge about the underlying mechanisms of change. And as stated nicely by McNally (2007): “Theoretical agnosticism about mediating mechanisms is acceptable only when treatment works with flawless fidelity”.

During the last two decades, the behaviour and cognitive theories have merged into what is referred to as the behavioural neuroscience of fear learning and memory. Instead of unpacking the artificial categorization of DSM disorders, it seeks general principles of fear learning and memory, which may finally turn into maladaptive behaviour (see also the Research Domain Criteria initiative of the National Institute of Mental Health). In addition to the behavioural and cognitive processes of fear learning and memory, also molecular, cellular and neural processes are incorporated. In this review, I will argue that a neuroscientific approach may improve our understanding of 1) the transition from normal fear into abnormal fear, and 2) the mechanisms of change in the treatment of pathological anxiety. Understanding the mechanisms

of change is crucial to delineate the necessary, optimal and boundary conditions for effective treatments. Here I present only a small selection of insights and observations from the huge body of Pavlovian fear conditioning research with a slight predominance of work from my own lab. The aim of the present paper is to illustrate the heuristic validity of behavioural neuroscience for understanding fear and anxiety disorders.

Associative fear learning and memory

Pavlovian fear conditioning serves a well-controlled experimental model to study associative fear learning and memory across a wide range of organisms (LeDoux, 1996; Rescorla & Holland, 1982). In a prototypical fear conditioning study, an innocuous and biologically neutral conditioned stimulus (CS), e.g., a tone or picture, acquires the capacity to elicit fear responses after the pairing with an intrinsically noxious or harmful unconditioned stimulus (US), e.g., electric stimulus. If the CS becomes a reliable predictor of the US, the CS will elicit species-typical conditioned behavioural responses (e.g., freezing in rats and potentiated startle reflex in humans).

Environmental cues indicating the unambiguous presence of an immediate threat give rise to intense fearful defensive behaviours ('fight or flight'), experimentally modelled by cue conditioning. Whereas more diffuse, distal or unpredictable threat cues produce sustained anxiety-like behaviour that is basically modelled by context conditioning (Phillips & LeDoux, 1992). Both the relatively short-lived situation-specific fearful responding and the more sustained anxiety are observed in the anxiety and related disorders such as PTSD (DSM-5) (American Psychiatric Association, 2013) and therefore relevant to be studied in translational research.

Decades of research in rodent models have provided tremendous insight into the neurobiology of fear and anxiety and the circumstances under which different defensive responses are recruited (Blanchard & Blanchard, 1998; Fanselow, 1994). Fear conditioning studies have consistently demonstrated that the amygdala is critically involved in the formation, consolidation and retrieval of associative fear memory (Davis, 1997; LeDoux, 1996, 2000). Neuroimaging research in humans corroborates the central role of the amygdala in associative fear learning (Büchel, Morris, Dolan, & Friston, 1998; Morris & Dolan, 2004), though a much broader network of brain areas is also critically involved (including the anterior cingulate cortex, hippocampus, insula, and vmPFC) (Mechias, Etkin, & Kalisch, 2010; Sehlmeyer et al., 2009; Visser, Scholte, & Kindt, 2011; Visser, Scholte, Beemsterboer, & Kindt, 2013; van Well, Visser, Scholte, & Kindt, 2012). Insights in the brain areas that are involved in fear learning and memory instigated further research on the molecular and cellular processes in those areas with a specific focus on the basolateral nucleus of the amygdala (Lamprecht & LeDoux, 2004).

An inherent restriction of memory research however, including fear conditioning, is that fear memory is not directly observable but can only be inferred from the degree to which conditioned responding during learning overlaps with the behaviour at later retention tests. Whereas the expression of fear during learning is certainly related to long-term memory, much of what we learn does not eventually transform into long-term memory. The dissociation between learning and memory has been most convincingly illustrated by studies in which pharmacological manipulations, administered immediately after learning, induced full amnesia at long-term, while leaving short-term memory intact (e.g., Miserendino, Sananes, Melia, & Davis, 1990; Schafe & LeDoux, 2000). Post-learning processes (i.e., off-line learning) account for this dissociation, as they induce the structural changes underlying the stabilization of a memory trace after its acquisition (i.e.,

consolidation; McGaugh, 1966). Whereas structural changes can be observed retrospectively, no signature exists that permits a reliable read-out of subsequent consolidation at the time of encoding (Dudai, 2012; but see Visser et al., 2013). If the focus of interest is to clarify processes of associative fear memory, the experimental design should by implication not only involve a fear conditioning phase but also a later retention test. The insight on off-line consolidation processes has changed the traditional design of human fear conditioning research: instead of assessing the retention of conditioned fear shortly after the acquisition phase, many studies currently include at least 24 h between those phases (e.g., Soeter & Kindt, 2011a).

The Pavlovian fear conditioning paradigm has not only proven its utility in understanding the origin of fear and anxiety disorders, it is also an excellent translational model to develop and advance treatment for these disorders (Mineka & Zinbarg, 2006). Though it should be noticed that anxiety disorders do not necessarily result from direct conditioning experiences such as traumatic events; they may also result from indirect or vicarious fear learning experiences, such as modelling or information transfer (Rachman, 1977) or even non-associative learning (Poulton & Menzies, 2002). But irrespective of the learning history, associative fear memory allegedly lies at the core of anxiety and related disorders (e.g., Panic Disorder, Phobia, PTSD) (DSM-5). People suffering from these disorders feel, think and act as if the feared stimulus (CS, e.g., physical symptoms such as heart palpitations) predicts the later occurrence of a negative outcome (US, e.g., feelings of losing control).

Of note, the Pavlovian fear-conditioning paradigm was originally developed to unveil general principles of fear learning and memory rather than pathological fear learning. Hence, the observations from the fear-conditioning paradigm neither in animals nor in humans can be directly translated to anxiety and related disorders. But the neurobiology of associative fear learning and memory may be informative on general underlying processes that go awry in those mental disorders. If we assume that irrational fears originate from an association between neutral and aversive stimuli (Mineka & Zinbarg, 2006), insights in the neurobiology of associative fear memory might also clarify the mechanisms of change in treatment of anxiety and related disorders.

Generalization and contextualization of fear memory

The ability to learn and remember which stimuli in the environment represent a threat clearly serves a survival mechanism of many species. Given that a known threat can take many forms, the learning and defensive behaviour should also extend towards other exemplars of the same semantic category that might foreshadow a similar aversive outcome (Dunsmoor, Martin, & LaBar, 2012; Mineka, 2002). By virtue of ensuing fast responding to novel potentially threatening stimuli fear generalization is functional, but it can turn into maladaptive behaviour when nonthreatening stimuli or contexts are inappropriately treated as harmful. Maladaptive fear generalization is indeed characteristic for anxiety disorders and PTSD (Glover et al., 2011; Grillon & Morgan, 1999; Lissek et al., 2005, 2009, 2010, 2014; Orr et al., 2000; Peri, Bean-Shakhar, Orr, & Shalev, 2000) and may explain the transition from normal to abnormal fear (Rosen & Schulkin, 1998). For example, when somebody has been bitten by a pit-bull, it is entirely functional to develop a fear for this dog and even if the learned fear generalizes to other similar dogs, we consider this as a functional fear generalization. Only when the fear generalizes to other animals that are somehow related to the original conditioned stimulus but in itself not threatening, we consider this as an irrational fear generalization. Research that is aimed to clarify which processes enhance fear generalization will ultimately help to answer the

fundamental question of why and how people differ in their dispositional vulnerability to develop abnormal fear behaviour.

Fear conditioning and fear generalization

The fear-conditioning paradigm enables to test the generalization of associative fear learning by assessing anxiety-like conditioned behaviour to other stimuli than the original reinforced stimulus (CS+). Systematic tests of generalization were initially developed in animals and later translated to humans. These tests assess conditioned fear responding to both CS+ and generalization stimuli, parametrically varying in similarity to the original CS+. The generalization stimuli represent a more ambiguous and uncertain source of threat than the original CS+ (Lissek et al., 2008). Generalization gradients or slopes are typically calculated, with the highest level of fear responding to the CS+ and decreasing levels of fear to generalization stimuli (e.g., Armony, Servan-Schreiber, Romanski, Cohen, & LeDoux, 1997; Lissek et al., 2008). Other studies assess fear responding to either a novel stimulus from the same semantic category as the original CS+, novel contexts, or the unreinforced safety signal (CS−) (e.g., van Ast, Vervliet, & Kindt, 2012; Soeter & Kindt, 2010, 2011b, 2012a, 2012b).

Whilst decades of animal conditioning research have focused on the perceptual similarity and discriminability of a conditioned stimulus (CS+), generalization is likely an active process of judging different sensory stimuli as being similar enough to predict the US (Shepard, 1987). Only recently, it became evident that fear generalization depends not solely on the physical properties of the CS+ and CS−, but also on the conceptual properties of the associative fear learning experience (Dunsmoor & LaBar, 2013; Dunsmoor, Mitroff, & LaBar, 2009; Dunsmoor et al., 2012; Soeter & Kindt, 2012a). Dunsmoor, Kragel, Marin, and LaBar (2013) showed fear generalization to super-ordinate categories but only after learning experiences with multiple exemplars of the same semantic object category. Also, the US intensity or the number of learning trials (CS+/US) determined fear generalization in rodents (Laxmi, Stork, & Pape, 2003), while increasing the fear intensity of the conditioned stimuli promoted fear generalization in humans (Dunsmoor et al., 2009). As to whether the intensity, or rather the negative valence of the outcome affects the generalization gradient is to be further investigated (Schechtman, Laufer, & Paz, 2010).

(Un)predictability, individual differences and fear generalization

Upon a fearful experience, we are automatically in search for predictors of the event in order to prepare for future encounters. If the outcome is perceived as more unpredictable, one may rely on a more generalized class of predictors in order to minimize the risk of 'missing' the catastrophe. Yet the notion that unpredictability of threat may foster fear generalization has received little attention in the fear conditioning literature (but see Laxmi et al., 2003), even though the unpredictability of threat is well recognized as a central feature of fear and anxiety disorders (Foa, Zinbarg, & Rothbaum, 1992; Grupe & Nitschke, 2013; Lake & LaBar, 2011). Most evidence on fear generalization of unpredictability regarding the aversive outcome (US) comes from studies on contextual anxiety (Grillon, Baas, Cornwell, & Johnson, 2006; Grillon, Cordova, Morgan Charney, & Davis, 2004; Vansteenwegen, Iberico, Vervliet, Marescau, & Hermans, 2008). In addition to this basic research on fear generalization in healthy individuals, patients with panic disorder and PTSD showed greater fear-potentiated startle responding in a temporally unpredictable aversive context compared to a predictable situation (Grillon et al., 2008). For future research on predictability and fear generalization, several promising candidates could be investigated, which are related to the probability, time and

nature of threat (Grupe & Nitschke, 2013), respectively: a) ambiguity in how likely a threat event is to occur, b) ambiguity in when an event will occur and c) experiential uncertainty of threat (e.g., Soeter & Kindt, 2012b). It bears mentioning that unpredictability of threat may also indirectly give rise to fear generalization by enhancing the aversive nature of the experience. Unpredictability in itself (i.e., without an explicit association with an aversive outcome) already increased anxiety-like behaviours (Herry et al., 2007). The aversive nature of unpredictability is further supported by repeated observations that animals consistently prefer predictable shocks and their associated contexts compared to unpredictable shocks (e.g., Fanselow, 1980; Grupe & Nitschke, 2013; Lake & LaBar, 2011; Mineka & Hendersen, 1985; Mineka & Kihlstrom, 1978). Thus, given the inherent uncertainty about potentially negative events in the future, a simple learned fear association may easily transfer to an overgeneralization of fear.

If fear generalization is a general consequence of fear learning in an uncertain environment, the question remains why only a minority of people is prone to exhibit maladaptive fear generalization. Obviously, the subjectively experienced unpredictability of threat has differential salience for different individuals. Most notably Eysenck (1965), followed by others (e.g., Mineka & Oehlberg, 2008), has postulated that personality characteristics may be systematically related to individual variation in abnormal associative fear learning, and in turn, to the pathogenesis of fear and anxiety disorders. For example, trait anxiety was specifically related to generalization of fear responding to the safety signal (CS−), but only after an unpredictable aversive event (US) (Kindt, Soeter, & Vervliet, 2009; Soeter & Kindt, 2010). Apparently, the unpredictable US may have rendered the CS+ a poor predictor in the high anxious individuals, while the low anxious individuals did not forget this specific fear association (CS−US) and showed differential fear responding to the CS+. Note that instead of fear generalization, the unpredictable US may have prompted stress sensitization in the high trait anxious individuals, given that we did not control for fear responding to other unrelated stimuli. Furthermore, other candidate traits (e.g., stress reactivity; Tellegen & Waller, 2008) for which future uncertainty is typically more aversive may also come to expression in the overgeneralization of fear (Gazendam et al., 2014).

Stress hormones and fear generalization

Another level of analysis involves the relation between stress hormones and the generalization of fear memory. Generalization of fear memory can also be operationalized as impaired contextualization of fear. Although there is ample evidence that the release of stress hormones during or after fear learning affects memory in a quantitative way (Wolf, 2009), an interesting question is whether stress hormones also affect fear memory more qualitatively by affecting processes of generalization to other stimuli and contexts different from the original learning episode.

A core neuroendocrine reaction in response to a fearful event is the rapid activation of the autonomic nervous system (ANS), which results in the release of norepinephrine in the brain, in part by neurons located in the locus coeruleus. These noradrenergic projections regulate neuronal function via β -adrenergic receptors in areas that are critically involved in fear learning and memory such as the amygdala and hippocampus (Foote, Bloom, & Aston-Jones, 1983; Gibbs & Summers, 2002; Roozendaal, McEwen, & Chattarji, 2009). Fearful experiences also stimulate activation of hypothalamus–pituitary–adrenal (HPA) axis, which leads to a slow increase in the release of glucocorticoid hormones from the adrenal cortex (corticosterone in most rodents; cortisol in humans). Glucocorticoid hormones enter the brain and bind to two subtypes of

discretely localized receptors: the mineralocorticoid receptor and glucocorticoid receptor, which are expressed in regions that are critical for memory formation such as hippocampus, amygdala, and prefrontal cortex (de Kloet, Joëls, & Holsboer, 2005; Krugers, Zhou, Joëls, & Kindt, 2011).

Cortisol and contextualization of fear memory

In a human contextual fear-conditioning paradigm, the administration of cortisol hydrocortisone (20 mg) prior to fear learning impaired the contextualization of fear responding in women, but the opposite pattern was found in men (van Ast et al., 2012). A noticeable limitation of this study was that we did not include a retention test for fear contextualization the other day. The rationale for studying the effect of cortisol on memory contextualization is that theories on the origin of PTSD emphasize impairment in the ability to bind fearful memories with their original encoding context (Acheson, Gresack, & Ribrough, 2012; Cohen & Zohar, 2004; Ehlers & Clark, 2000; Liberzon & Sripada, 2008). Since patients suffering from PTSD exhibit augmented memory generalization (Elzinga & Bremner, 2002), contextualization of their trauma memories seems to be compromised in these patients. The hippocampus, which is supposed to subserve context effects on memory (Davachi, 2006; Kalisch, Wiech, Critchley, & Dolan, 2006; Rasch, Büchel, Gais, & Born, 2007), is a main target of glucocorticoids (Joëls & Baram, 2009). In order to test a more valid translational model for PTSD, retention of long-term fear expression should be tested as well.

Also animal research has begun to explore how stress or corticosteroids may alter the contextualization of fear memory by targeting the hippocampus. One study in rats showed that exposure to traumatic stressors (e.g., predator scent stress and underwater trauma) impaired the recall of contextual specificity of their fear responding (Cohen, Liberzon, & Richter-Levin, 2009). To test the ability of animals to learn and remember contextual cues, the authors devised a differential contextual odour-conditioning paradigm. The two stress manipulations abolished the ability to modulate their fear responses based on contextual cues, both when stress exposure preceded odour discrimination training and when it followed successfully completed training. In another very elegant study, glucocorticoids were infused into the dorsal hippocampus of mice immediately after fear conditioning with three footshock intensities (0.3, 0.5 and 0.8 mA), both in a cue-conditioning and context-conditioning group (Kaouane et al., 2012). In the cue-conditioning group, corticosterone did not modify fear responding (i.e. freezing), which supports the notion that the hippocampus is not necessary for cue conditioning in rodents (Kim & Fanselow, 1992; Phillips & LeDoux, 1992). In the context-conditioning group, however, the corticosterone injected after the lowest shock intensity (0.3 mA) enhanced conditioned fear to the context. But the most crucial finding was that when corticosterone followed the highest shock intensity (0.8 mA), PTSD-like memory impairments appeared. Animals did not freeze in response to the correct context predictor of the threat, but in response to the tone. These animals also showed a fear response to a cue (2 kHz tone) not previously experienced but which was perceptually similar to the one experienced during fear conditioning (1 kHz tone). The observation that corticosterone only prompted fear generalization in the high intensity group may be explained by a putative interaction with the noradrenergic system. There is convincing evidence that arousal-related activation of the noradrenergic circuitry within the basolateral amygdala is a necessary prerequisite for corticosteroid effects on learning and memory (Roozendaal, Okuda, Van der Zee, & McGaugh, 2006). In other words, the infusion of glucocorticoids into the hippocampus after fear conditioning decreased

the ability to restrict fear to the appropriate predicting stimuli (Kauouane et al., 2012). Such animal studies may be considered as a paragon for translational research because they provide an explanation for the impaired contextualization of trauma memory in PTSD. Yet, the data are not in line with some observations in clinical populations.

Studies in trauma victims have shown that reduced cortisol responses after trauma were associated with increased risk of developing subsequent PTSD (Yehuda, Resnick, Schmeidler, Yang, & Pitman, 1998), while victims who were administered cortisol following trauma were less susceptible to develop full-blown PTSD symptoms (Schelling et al., 2004). Observations like these have prompted the idea that corticoids may in fact protect against the development of PTSD, as opposed to the alleged detrimental effect. In this respect, a robust cortisol response to impending threat is a highly adaptive response. These contrasting findings exemplify that behavioural neuroscience research in animals cannot be directly translated to clinical practice. Research into the modulatory effects of stress hormones on associative fear learning and memory is rather complex and still in its infancy. Crucial factors are involved in the qualitative and quantitative effects of glucocorticoids on fear memory; among them are sex differences (Dalla & Shors, 2009), the interaction with norepinephrine (Roozendaal et al., 2009), timing of corticosteroid administration relative to the learning phase given the differences between acute and slow, presumably genomic, effects of corticosteroids (van Ast, Cornelisse, Meeter, Joëls, & Kindt, 2013; Cornelisse, Van Ast, Haushofer, Seinsträ, & Joëls, 2013; Joëls, Fernandez, & Roozendaal, 2011; Krugers et al., 2011). Also, lasting inter-individual differences due to variation in early life stress and/or dispositional emotional arousal (noradrenergic activation) may moderate the effect of glucocorticoids on the neuroplasticity of fear learning and memory (Champagne et al., 2008; Weaver et al., 2004). A step-by-step research program that incorporates these pertinent parameters might eventually clarify this domain of research.

Noradrenaline and generalization of fear memory

There is scarce but unequivocal evidence of the noradrenergic involvement in fear memory generalization. Administering yohimbine (10 mg) to human participants before they were fear-conditioned resulted in a strong enhancement of fear generalization 48 h later to cues that were not encountered during fear learning, but which belonged to the same semantic category as the original conditioned stimulus (Soeter & Kindt, 2012a). Yohimbine is an α_2 -adrenergic auto-receptor antagonist that increases central noradrenergic transmission (Tam, Worcel, & Wyllie, 2001). We know from animal literature that yohimbine HCl induced pCREB activation (i.e., cAMP response element binding phosphorylation) (Sun et al., 2010), and that p-CREB is not only involved in the formation of associative fear memory (Davies et al., 2004; Josselyn et al., 2001) but also in the generalization of fear memory (Han et al., 2008). These findings nicely illustrate how different levels of analysis (i.e., behavioural, cellular and molecular) may converge and deepen the understanding of fear memory generalization.

Neural read-outs of fear generalization

In addition to the behavioural expression of fear memory, future research might also pursue on recently developed neural read-outs of fear generalization. Unlike the traditional analysis of mean activation in fMRI research, multivoxel pattern analysis (MVPA) yields a distinctive stimulus signature that can be used to assess semantic similarity, thereby providing a tool to examine how the brain categorizes information (Haxby et al., 2001; Kriegeskorte,

Mur, & Bandettini, 2008; Norman, Polyn, Detre, & Haxby, 2006; Polyn, Natu, Cohen, & Norman, 2005). MVPA is a novel technique to analyse distributed patterns of blood oxygen level-dependent magnetic resonance imaging (BOLD MRI) data. It offers the opportunity to meticulously assess fear-learning dependent changes, but more importantly, to assess the formation of complex associative fear networks as opposed to simple fear associations (Dunsmoor et al., 2013; Visser et al., 2011, 2013).

Persistence of fear memory

In reaction to real or imagined threat fears are generally considered an integral and adaptive part of normal development. Fears wax and wane and although they usually disappear in due course, in some individuals they persist and come to interfere with daily functioning such as in anxiety disorder and PTSD (Ollendick, King, & Muris, 2002). Hence, the transition from normal fear to pathological fear may also be characterized by the *persistence* of fear responding while the threat is no longer present. This has become most evident in prospective studies where trauma victims usually report intense fear responses in the first weeks after experiencing a trauma, but only a proportion of victims show persistent symptoms and develop chronic PTSD (e.g., Murray, Ehlers, & Mayou, 2002; Riggs, Rothbaum, & Foa, 1995; Rothbaum & Foa, 1993; Rothbaum, Foa, Riggs, Murdock, & Walsh, 1992). Persistent PTSD occurs only when individuals process the past traumatic event and/or its sequelae in a dysfunctional way that produces a sense of a serious current threat (Ehlers & Clark, 2000).

Anxiety and impaired fear extinction

The fear-conditioning paradigm also provides an excellent heuristic platform to study individual differences in the persistence of fear. The most straightforward operationalization may be extinction learning, where the CS is no longer followed by an aversive event. The importance of research on extinction learning is fully recognized because it is the experimental model for exposure treatment. Still, a relevant question that remains to be answered is whether insights on extinction learning will help to understand why people differ in their dispositional vulnerability to develop pathological fears.

Although extinction (i.e., repeated nonreinforced re-exposure to the CS) is a very effective strategy to reduce a previously learned fear response, a consensus has been building that extinction learning does not destroy the original fear memory. Instead it involves the formation of a new inhibitory memory that competes with the excitatory fear memory generated during fear conditioning (Bouton, 1993; LeDoux, 1995). Once a fear association has been learned, the fear memory is supposed to be forever.

Two lines of evidence substantiate the notion that extinction memory involves the formation of new memory as opposed to erasing the original fear memory. First, there are a vast number of animal and human studies showing that fear memory (CS– > US) remains available after successful fear extinction and that it can be uncovered by a variety of retrieval techniques: the confrontation with unsignaled USs (i.e., reinstatement), a context change (i.e., renewal), or the passage of time (i.e., spontaneous recovery) (Baum, 1988; Bouton, 2002; Bouton & Bolles, 1979; Rescorla, 2001; Rescorla & Heth, 1975). In other words, extinction is mainly expressed in the context in which extinction was given, and even in that context, fear responses will either spontaneously recover over time or return when fear memory is triggered by unpredictable aversive events (Quirk, 2002). In addition to context specificity, extinction seems also to bind to the unique features of the stimulus under extinction (Lovibond, Davis, & O'Flaherty, 2000; Vervliet,

Kindt, Vansteenwegen, & Hermans, 2010; Vervliet, Vansteenwegen, & Hermans, 2010; Vervliet, Vansteenwegen, Hermans, & Eelen, 2007). Hence, extinction memory is much weaker than fear memory: while generalization of fear extinction is difficult to achieve, fear learning easily transfers to other contexts and stimuli. This marked asymmetry between fear learning and extinction implies that biology has deemed it better to fear than not to fear (Maren & Quirk, 2004).

More support for the view that extinction does not erase the fear memory comes from the literature on the different neural substrates that are involved in fear learning and extinction. Both lesion studies in animals and the somewhat more controversial neuroimaging literature in humans demonstrate that the amygdala is involved in the formation, consolidation and retrieval of fear memory (Lamprecht & LeDoux, 2004), while the hippocampus and ventral medial prefrontal cortex (vmPFC) are key areas for the formation and retrieval of extinction memory, respectively (Milad, Rauch, Pitman, & Quirk, 2006; Rauch, Shin, & Phelps, 2006; Sehlmeier et al., 2009; Sotres-Bayon, Cain, & LeDoux, 2006).

Anxiety disorders and deficits in fear inhibition

There is ample evidence that individuals who are at risk for developing fear and anxiety disorders – either by their very nature or due to personal circumstances – display impairments in extinction learning (e.g., Craske et al., 2008; Gazendam, Kamphuis, & Kindt, 2013; Grillon & Ameli, 2001; Liberman, Lipp, Spence, & March, 2006; see for a review Lissek et al., 2005), though this finding is not unequivocal (e.g., see for null findings Fredrikson & Georgiades, 1992; Otto et al., 2007; Pineles, Vogt, & Orr, 2009; Torrents-Rodas et al., 2012). Also, patients who already developed an anxiety disorder exhibit impaired extinction learning (Blecher, Michael, Vriends, Margraf, & Wilhelm, 2007; Michael, Blecher, Vriends, Margraf, & Wilhelm, 2007; Norrholm et al., 2011; Orr et al., 2006; Pitman & Orr, 1986), or reduced extinction memory (Milad et al., 2008).

The observations that individuals who are at risk for abnormal fears are characterized by impaired extinction corroborate the hypothesis of neural substrates of impaired fear inhibition as a biomarker for the development of anxiety and related disorders (Davis, Falls, & Gewirtz, 2000). As such, the neurobiological insights on inhibitory learning might eventually help to decipher the aberrant processes in individuals at risk. It should be noted however that the traditional fear-conditioning paradigm essentially falls short in distinguishing between excitatory and inhibitory learning. The competition between the original excitatory fear association and the newly formed inhibitory memory trace determines the behavioural outcome of extinction learning (Maren & Quirk, 2004; Myers & Davis, 2004). Hence, impaired extinction learning is not necessarily due to deficits in inhibitory learning but may also be the result of enhanced excitatory learning during fear conditioning (e.g., Bouton, 1993). In a recent study, utilizing the AX+/BX-conditional discrimination paradigm that allows for the independent evaluation of fear excitation and fear inhibition (Jovanovic et al., 2005; Myers & Davis, 2004), we did not find convincing evidence that individuals at risk for anxiety display impaired fear inhibition (Kindt & Soeter, 2014; but see Jovanovic et al., 2009, 2010).

Furthermore, in two independent human fear-conditioning studies we convincingly demonstrated that strengthening the formation of fear memory by a noradrenergic manipulation resulted in impaired extinction learning 48 h later (Soeter & Kindt, 2011a, 2012a). Interestingly, the administration of yohimbine HCl before fear conditioning did not directly augment conditioned fear responding, but only came to expression in impaired extinction

learning and a stronger recovery of fear two days later. Based on these observations, it may be suggested that the transition between normal and abnormal fear may also be explained by enhanced excitatory learning as opposed to impaired inhibitory learning. In view of the 'off-line' processes of memory consolidation, which may take hours to days (Lamprecht & LeDoux, 2004), the highly controlled fear-conditioning paradigm may not be suitable to detect those fear enhancing effects during testing.

A challenge for the cognitive account

From prospective studies in trauma victims it is known that initial fear responding in the aftermath of a traumatic event is very common and a poor indicator of symptom development or PTSD diagnosis (e.g., Murray et al., 2002; Riggs et al., 1995; Rothbaum & Foa, 1993; Rothbaum et al., 1992). Rather processes such as negative interpretation of the typical fear responses (i.e., intrusive memories) or other psychological processes during or after the traumatic event (e.g., dissociation, mental defeat) are predictive of chronic symptoms (Ozer, Best, Lipsey, & Weiss, 2003). However, the lack of evidence for individual differences in the immediate fear response to a traumatic event may also be due to the utilized self-report measurements, which are clearly not sufficiently sensitive to gauge the underlying neurobiological processes.

An alternative explanation for PTSD may be that elevated noradrenaline levels during or shortly after a traumatic experience may strengthen the consolidation of trauma memory. It warrants emphasis that this conjecture mainly serves as an illustration of how the prevailing cognitive theory on anxiety disorders and PTSD does not yet incorporate insights from the neuroscience literature. Elevated noradrenaline triggered by the traumatic event may prompt the structural changes underlying the consolidation of associative fear memory (Hu et al., 2007). These processes are not necessarily reflected in stronger fear symptoms, traditionally measured by self-reports. In our fear conditioning study in healthy individuals we did not even observe a direct effect of the noradrenergic enhancement on the physiological expression of fear during the conditioning phase (Soeter & Kindt, 2011a, 2012a). The noradrenergic manipulation only came to expression at a later retention test when the drug was already washed out. Hence, the increased noradrenaline release during or shortly after fear learning strengthened the later processes of memory consolidation. This resulted in an enhanced generalization and persistence of associative fear memory: two potentially interesting markers of abnormal fear learning. Individual differences in the neurobiological response pattern triggered during/or after trauma exposure might therefore be a plausible alternative explanation for the development of PTSD. The individual differences may either be a result of variation in genetic make-up and/or variation in past experiences, given that elevated levels of norepinephrine have been observed in individuals with a history of trauma (Geraciotti et al., 2001; Otte et al., 2005).

In sum, the fear-conditioning model provides a well-controlled and fine-grained research platform to further examine fear generalization and persistence of associative fear memory as intermediate phenotypes of anxiety disorders. But even the current fear-conditioning paradigm encounters difficulty to detect the off-line processes of memory consolidation, which might eventually be crucial for the generalization and persistence of fear.

Novel therapeutic interventions targeting the underlying processes of (re)learning

In daily life we commonly associate memory with the past, but memories are constructed mostly for the sake of acting in the present and future. Experience-dependent alterations in the

individual's behaviour draw on the past to permit better-adapted responses to on-going reality and the future. The capacity to anticipate clearly endows human beings with significant advantages. Under certain contextual conditions our brain seems to be able to do just that (Dudai, 2009).

A dynamic balance between stability and plasticity of memory appears crucial for adaptation to an ever-changing environment. Stability of fear memory guarantees a fast response to threat and does not require continuous re-learning, whereas plasticity permits modification of an established memory trace, should conditions require such adaptation (Lee, 2009). Plasticity of fear memory is also of great clinical importance, as it provides a window of opportunity to target unwanted, excessive emotional memories such as those that underlie anxiety and other fear-related disorders.

In the laboratory there are basically two approaches to dampen the expression of a previously formed fear memory. First, the most extensively studied and well-known procedure is extinction training. Although extinction-like exposure treatments are among the most effective strategies for treating anxiety and related disorders, there are still many patients who experience a relapse even after initially successful treatment (Vervliet, Craske, & Hermans, 2013). The prevailing view on the return of fear is that extinction solely involves the formation of a new inhibitory memory whilst the fear memory itself remains intact (Bouton, 1993). From an evolutionary perspective, it is extremely functional to keep fear memory as it is. However, the putative indelibility of fear memory can also be harmful and maladaptive, such as in anxiety disorders and PTSD. One way to counteract the return of fear is by identifying therapeutic strategies for enhancing inhibitory learning, as this form of learning is the basis of CBT for fear and anxiety disorders (Craske et al., 2014). A number of so-called cognitive enhancers have been uncovered, including yohimbine that increases central noradrenergic transmission (Tam et al. 2001). Following an initial report of several years ago where yohimbine facilitated extinction in mice (Cain, Blouin, & Barad, 2004), recent studies have shown moderate to mixed effects of yohimbine as adjunct to extinction learning (Holmes & Quirk, 2010; Smits et al., 2014). An important limitation of this novel strategy is that it does not eradicate the original fear memory: The conditioned fear response returned when the animals were tested outside of the extinction context (Morris & Bouton, 2007). The most extensively studied pharmacological adjunct for CBT however is D-cycloserine (DCS), a partial agonist at the glycine site of N-methyl-D-aspartate (NMDA) glutamate receptors (Bowery, 1987; Hood, Compton, & Monahan, 1989). The two observations that 1) extinction learning is NMDA receptor dependent (Falls, Miserendino, & Davis, 1992) and 2) DCS enhanced the retention of fear extinction (Walker, Ressler, Lu, & Davis, 2002) prompted fear conditioning research as well as clinical trials. A growing body of literature indeed showed that DCS targeting the consolidation of inhibitory memory might improve the long-term efficacy of CBT (see for extensive reviews of the literature, Graham, Callaghan, & Richardson, 2014; Milad, Rosenbaum, & Simon, 2014). Even though DCS emerges as a potential augmentation strategy for CBT, the beneficial effect of DCS depends on successful within-session extinction and is again (like yohimbine) restricted to the context in which extinction is learned (Bouton, Vurbic, & Woods, 2008; Hofmann, Wu, & Boettcher, 2013; Woods & Bouton, 2006). Hence, the discovery of cognitive enhancers (e.g., DCS, yohimbine) may be promising by accelerating treatment effectiveness, but they do not prevent the return of fear since they leave the fear memory intact.

The (re)discovery in the neuroscience literature that fear memory in animals is not necessarily permanent but can change when retrieved – a process referred to as memory reconsolidation – may therefore be a promising alternative. It not only enables to diminish

conditioned fear responding but it may also affect the associative fear memory itself, which might eventually solve the problem of relapse. Reconsolidation involves a two-phase process where consolidated memories may temporarily return into a labile state, requiring gene transcription, de novo protein and RNA synthesis for restabilization (Dudai, 2004; Lee, 2009; Nader, Schafe, & LeDoux, 2000; Sara, 2000; Tronson & Taylor, 2007). It describes the fundamental finding that the retrieval of a previously stable memory renders that memory vulnerable to the disruptive effects of amnesic agents.

Disrupting reconsolidation of fear memory by a noradrenergic β -blocker

Amnesia for learned fear has been demonstrated in animals by drugs (e.g., anisomycin) targeting directly the required protein synthesis or indirectly by the noradrenergic β -blocker propranolol, which is supposed to inhibit the noradrenaline-stimulated CREB phosphorylation (Chaundhry & Granneman, 1999; Debiec & LeDoux, 2004; Jockers et al., 1998; Thonberg, Fredriksson, Nedergaard, & Cannon, 2002). Evidence for disrupting reconsolidation of fear memory recently progressed from animals to humans (Kindt et al., 2009; Sevenster, Beckers, & Kindt, 2012a, 2013; Soeter & Kindt, 2010, 2011b, 2012a). In a human discriminative fear-conditioning paradigm, we consistently demonstrated that a β -adrenergic receptor antagonist (i.e., 40 mg propranolol HCl) administered either *prior to* or *after* memory reactivation effectively diminished the conditioned fear response and prevented the return of fear in healthy participants. The repeated observations that memory retrieval techniques – exposure to primary reinforcers (reinstatement), a change in context (renewal) or simply the passage of time (spontaneous recovery) – did not lead to the re-emergence of fear memory expression as is generally observed after extinction training, support the superiority of disrupting reconsolidation over extinction learning.

Proof of principle

The basic design that we utilized in our studies on disrupting reconsolidation of fear memory in healthy participants includes testing over different phases mostly across three consecutive days (see Fig. 1). *On day 1* – in the *fear acquisition phase*, the participants are exposed to a series of picture presentations. One fear-relevant stimulus (CS1+) is repeatedly paired with an aversive electric stimulus (US), resulting in the acquisition of a fear association, whereas another fear-relevant stimulus (CS2–) is never followed by an US. *On day 2* – in the *memory reactivation phase*, the re-exposure to the conditioned stimulus (CS1) typically triggers a threat expectation and a concomitant conditioned fear response. For memory destabilization, activation of the fear memory is necessary though not sufficient (Forcato, Argibay, Pedreira, & Maldonado, 2009; Forcato, Rodriguez, Pedreira, & Maldonado, 2010; Lee, 2009; Pedreira, Pérez-Cuesta, & Maldonado, 2004; Sevenster et al., 2012a). Pursuing on the idea that the function of reconsolidation is to update the memory trace to an ever-changing environment (Lee, 2009), the memory reactivation should also involve a discrepancy between what has already been learned and what can be learned on a given retrieval session (i.e., *prediction error*). Depending on the learning history, the reactivation trial may consist of either an unreinforced (CS1–) or a reinforced (CS1+) trial (Sevenster et al., 2013). In this phase, we systemically administer 40 mg propranolol HCl, a β -adrenergic receptor antagonist that indirectly targets the protein synthesis required for reconsolidation (Thonberg et al., 2002). In view of the peak plasma concentrations of propranolol HCl (Gilman & Goodman, 1996), we administered an oral dose of 40 mg of propranolol HCl 90 min prior to the

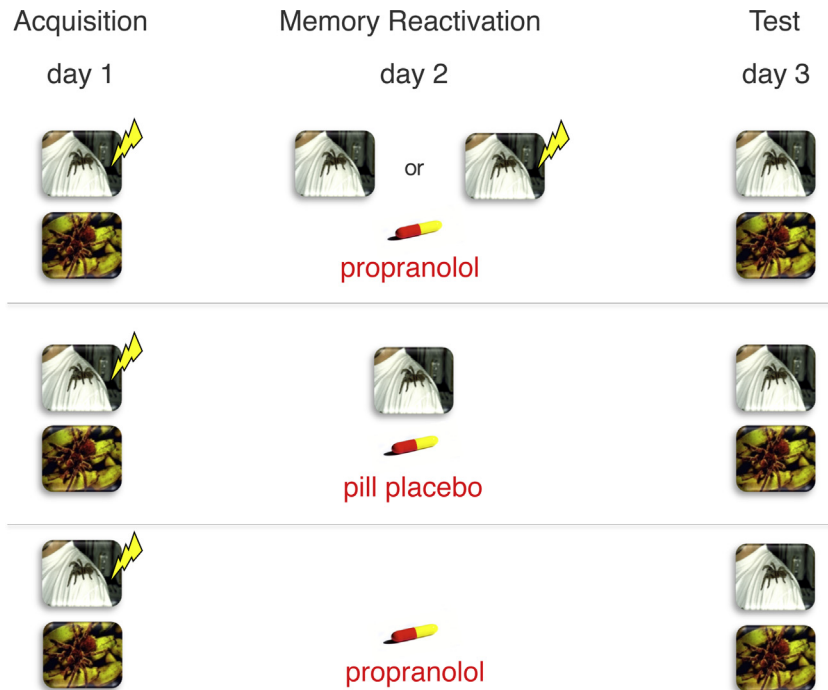


Fig. 1. Schematic representation of a prototypical human fear-conditioning design on disrupting reconsolidation of associative fear memory. *Fear acquisition* (day 1): a fear-relevant stimulus (CS1+) is repeatedly paired with an aversive electric stimulus (US), whereas another fear-relevant stimulus (CS2–) is never reinforced. *Memory reactivation* (day 2): re-exposure to the fear conditioned stimulus (CS1+/-) either preceded or followed by the systemic administration of the noradrenergic β -blocker propranolol HCl (40 mg) (double-blind/placebo-controlled), or systemic administration of propranolol HCl without memory reactivation. *Test* (day 3): repeated unreinforced presentations of the conditioned stimuli (CS1– and CS2–) followed by situational triggers (e.g., unpredictable US) to test for the return of fear.

reactivation of the fear memory in our first experiments (day 2). Administering pills prior to reactivation does not rule out a possible effect of the pharmacological manipulation on the retrieval of the fear memory itself. Therefore, in our latter experiments, we always administered propranolol HCl *after* memory reactivation, yielding similar results. *On day 3* – in the *memory test phase*, the behavioural fear expression is tested 24 h after the intervention (i.e., first test trial day 3), followed by an extinction procedure and situational triggers to test for the return of fear (i.e., reinstatement, renewal, spontaneous recovery 1 month later).

In a series of consecutive experiments in independent samples (Sevenster et al., 2012a, 2013; Sevenster, Beckers, & Kindt, *in press*; Soeter & Kindt, 2010, 2011b, 2012a experiment I & II, 2012b; but see Bos, Beckers, & Kindt, 2014) we consistently replicated our original finding of disrupting reconsolidation of fear memory by a β -adrenergic blocker propranolol HCl (Kindt et al., 2009). Interestingly, the manipulation affects the potentiation of the startle reflex, whilst the cognitive expression of fear memory (i.e., US expectancy ratings) and conditioning of the skin conductance response (SCR) remain unaffected. Disrupting reconsolidation of fear memory by the β -adrenergic blocker propranolol HCl seems to interfere with the less conscious expression of associative fear memory, given that conditioning of the SCR depends on awareness of associative fear learning, whereas the startle potentiation is relatively insensitive to awareness and instructions (Sevenster, Beckers, & Kindt, 2012b, 2014b). In addition to the above-mentioned replications, we also extended our initial fear erasing effect by testing several boundary and necessary conditions for disrupting reconsolidation.

Translation to clinical practice

In a recent study we translated the laboratory findings from fear conditioning research to a subclinical trial with spider phobic

individuals. We showed that a very short exposure to a tarantula (2 min) followed by the intake of 40 mg propranolol HCl (double blind placebo-controlled) was effective in reducing spider fear behaviour (Soeter & Kindt, *unpublished results*). In fact, the active intervention transferred avoidance behaviour into approach behaviour in all participants and the effect maintained at 3-months and 1-year follow-up, while the placebo group and the propranolol HCl group without memory reactivation (i.e., no confrontation with the spider) did not improve at all. In line with the fear-conditioning studies, the intervention exclusively changed the fear behaviour without initially affecting the cognitive expression of spider fear. However, a reduction in dysfunctional spider fear beliefs followed the behavioural change at 3-months follow. This observation is in stark contrast with the cognitive theory of anxiety disorders. According to this theory, dysfunctional interpretations and beliefs lie at the core of anxiety disorders and changing those beliefs is necessary for an effective treatment.

Apparently, this is only a first step in translating laboratory findings to clinical practice. Also pilot studies from other labs in patients with PTSD seem to be promising (Brunet et al., 2008; Brunet et al., 2011), though it bears mentioning that these studies were not optimally designed to trigger memory reconsolidation (i.e., prediction error). Future research is necessary to critically test whether these preliminary clinical observations are substantiated in larger groups of people who suffer from severe anxiety and related disorders.

Conceptual and methodological limitations

If we speculate on translating these laboratory findings into clinical practice, several issues and potential limitations are to be considered. First, it may be questioned whether a pharmacological manipulation by the noradrenergic β -blocker is really necessary to

disrupt the process of reconsolidation or whether a behavioural procedure aimed to interfere with reconsolidation would yield a similar neutralizing effect. Even though a one-session treatment of a low dose of propranolol is clearly nontoxic, an entirely behavioural procedure is always preferable over a pharmacological intervention, provided that similar effects can be obtained. There is indeed an alternative method where extinction training is presented within the window of reconsolidation in rodents (Clem & Huganir, 2010; Monfils, Cowansage, Klann, & LeDoux, 2009) and humans (Agren, Furmark, Eriksson, & Redrikson, 2012; Oyarzún et al., 2012; Schiller et al., 2010). Because memory retrieval techniques (i.e., renewal, reinstatement, spontaneous recovery) did not recover the conditioned fear responding, extinction within the reconsolidation window may also target the process of memory reconsolidation. Several animal and human studies failed however to replicate the original findings by Monfils et al. (Chan, Leung, Westbrook, & McNally, 2010; Golkar, Bellander, & Öhman, 2012; Kindt & Soeter, 2013; Soeter & Kindt, 2011b).

A second issue concerns the optimal conditions to trigger memory reconsolidation. The memory reactivation session seems procedurally similar to extinction training (i.e., unreinforced exposure), but it should be much shorter than extinction (Bos, Beckers, & Kindt, 2012; Sevenster et al., *in press*). The window of opportunity to target emotional memory with amnesic agents is small, since it is preceded and followed by phases that leave the original memory unaffected. Even though the fear reducing effects are very robust and promising for the development of reconsolidation-based treatments, the success of the manipulation depends on subtle differences in the reactivation procedure (Merlo, Milton, Goozée, Theobald, & Everitt, 2014; Sevenster et al., 2013, *in press*).

A third issue involves the dissociation between mechanisms mediating the behavioural expression of fear from those that mediate the process of *reconsolidation* (e.g., Balderas, Rodriguez-Ortiz, & Bermudez-Rattoni, 2013; Ben Mamou, Gamache, & Nader, 2006; Caffaro, Suarez, Blake, & Delorenzi, 2012; Cocoz, Maldonado, & Delorenzi, 2011; Rodriguez-Ortiz, Balderas, Garcia-Delatorre, & Bermudez-Rattoni, 2012; Sevenster et al., 2012a, 2013, *in press*). We observed that mere retrieval of the fear memory is not sufficient to induce its labilization and subsequent reconsolidation (Sevenster et al., 2012a, *in press*). In other words, fear expression during memory reactivation is not informative on whether the memory trace enters a labile phase. Recent animal studies clarify this behavioural dissociation by discovering differential and dissociable receptors in the basolateral amygdala mediating the expression, destabilization and restabilization of previously conditioned fear memories (e.g., Barreiro, Suarez, Lynch, Molina, & Delorenzi, 2013; Milton et al., 2013). Given that memory *destabilization* is a prerequisite for the noradrenergic β -blocker to interfere with the process of *restabilization*, an important question is how we can infer successful memory destabilization in clinical practice. Actually, we uncovered that prediction error – operationalized by a mismatch between what was expected and what actually occurred – could serve as an independent index for memory destabilization independent from the fear expression itself (Sevenster et al., 2013). The results indicate that the occurrence of a prediction error is a necessary condition for reconsolidation and provides a useful instrument for developing and optimizing reconsolidation-based treatments for patients suffering from fear and anxiety disorders in the future. Notwithstanding these new insights, no objective criterion is yet available to determine the optimal degree of prediction error in clinical practice.

A more general challenge for translating the neuroscience literature into clinical practice concerns the ecological validity of the fear-conditioning paradigm. The evidence for disrupting

reconsolidation has mainly been shown in animals and humans for relatively new (one day old) and simple fear memories (i.e., tone $\rightarrow$ shock; picture $\rightarrow$ shock). It is not self-evident that disrupting reconsolidation of older, stronger and broader memory networks is as effective as it has been shown in the laboratory for cued fear conditioning. Also with respect to the conditioned fear behaviour it is still unclear whether the observations from the animal and human laboratory studies generalize to patients with fear and anxiety disorders. The fear reducing effects are thus far mainly demonstrated for freezing in rodents or physiological responding in humans, with only one exception where we demonstrated that also the subjective feelings of distress were significantly neutralized by noradrenergic blockade of memory reconsolidation (Soeter & Kindt, 2012b). It may be questioned whether these fear-reducing effects in the laboratory are indicative of the typical experiences of fear and avoidance behaviour characteristic of patients with anxiety disorders and PTSD. It has even been suggested that the terms “fear conditioning” and “conditioned fear responding” should be avoided as it blurs the distinction between on the one hand processes that give rise to the conscious feelings of fear in patients with anxiety disorders and on the other hand the non-conscious processes that control defensive responses elicited by threats or conditioned stimuli in the laboratory (LeDoux, 2014). Indeed, conditioned fear responding does not have a “telltale signature” of the fearful feelings characteristic for fear and anxiety disorders (LeDoux, 2014). But the defensive startle reflex is a response preparation and may be considered as a measurement of an action tendency of fear and anxiety, a central feature of emotions (Frijda, 1986). Future research should investigate whether the current findings indeed generalize to excessive fears and avoidance behaviour in individuals suffering from anxiety and related disorders.

To recap, cognitive behavioural interventions have demonstrated long-term efficacy in the treatment of fear and anxiety disorders. Several of these interventions may already capitalize on processes of fear memory reconsolidation. However, the issue of whether specific interventions (e.g., behavioural experiments, imagery rescripting, EMDR) either weaken the original fear memory or whether a new extinction memory is formed is currently unresolved. Treatment effect studies are not suited to answer this question. Though restrictive by its very nature, translational research may at least advance our understanding of the mechanisms of change.

Summary

The Pavlovian fear-conditioning paradigm is an excellent tool to decipher the neurobiology of fear learning and memory, with the considerable potential of cutting across a wide range of organisms. The fact that we can translate clinical observations into testable hypotheses at different levels of analysis invigorates the field of fear and anxiety disorders. Several observations were selected from the animal and human literature to illustrate how the behavioural neuroscience has begun to unravel the neurobiological mysteries of associative fear learning and memory. Although the traditional fear conditioning paradigm typically models normal fear learning rather than pathological processes, research on the generalization and persistence of associative fear memory shows its heuristic utility for understanding anxiety and related disorders. Furthermore, the recent insights on disrupting the reconsolidation of fear memory both in animals and humans open up new avenues for providing a long-term cure for patients suffering from irrational fears. The observation that the cognitive level remained unaffected and only followed the behavioural change, poses a challenge to the cognitive account of emotional disorders. Finally, the apparent

dissociation between the expression and malleability of fear memory is a crucial insight for clinical practice, given that fear responding is the sole read-out for therapist and patient. Albeit restrictive, a reductionist analytic approach is advocated at this stage, given that we are far from understanding how normal fear may turn into abnormal fear, nor do we truly understand the mechanisms of change in treatment of fear and anxiety disorders. Nonetheless, the laboratory findings on the molecular and cellular level of fear learning and memory cannot be easily translated to the complex level of emotional memory in psychiatric disorders. In the future, the neuroscience arena of associative fear learning and memory requires a more synthetic approach that seeks to integrate the different levels of analysis into a cohesive and comprehensive theory.

Conflict of interest

The author declares no conflict of interest.

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