



What's wrong with fear conditioning?☆

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ABSTRACT

Fear conditioning is one of the prime paradigms of behavioural neuroscience and a source of tremendous insight in the fundamentals of learning and memory and the psychology and neurobiology of emotion. It is also widely regarded as a model for the pathogenesis of anxiety disorders in a diathesis-stress model of psychopathology. Starting from the apparent paradox between the adaptive nature of fear conditioning and the dysfunctional nature of pathological anxiety, we present a critique of the human fear conditioning paradigm as an experimental model for psychopathology. We discuss the potential benefits of expanding the human fear conditioning paradigm by (1) including action tendencies as an important index of fear and (2) paying more attention to “weak” (i.e., ambiguous) rather than “strong” fear learning situations (Lissek et al., 2006), such as contained in selective learning procedures. We present preliminary data that illustrate these ideas and discuss the importance of response systems divergence in understanding individual differences in vulnerability for the development of pathological anxiety.

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Pavlovian fear conditioning is amongst the most successful laboratory paradigms in the history of experimental psychopathology. Modelled after the appetitive conditioning procedure introduced by Pavlov (1903/1928, 1927), it entails the repeated pairing of an initially neutral stimulus (the conditioned stimulus or CS; say, a tone) with a stimulus that is intrinsically aversive (the unconditioned stimulus or US; say, an electrocutaneous stimulus). As a result, CS presentation typically comes to elicit a variety of reactions indicative of fear. In animals, these responses may include the interruption of all locomotion and gross body movements during the presentation of the CS (freezing; e.g., Bouton and Bolles, 1980), suppression of ongoing instrumental behaviour (the so-called conditioned emotional response; Davis, 1990), and amplification of the startle reflex that is elicited by a loud auditory probe (startle potentiation; e.g., Brown et al., 1951). In humans, next to physiological indices of fear (e.g., an increase in skin conductance during presentation of the CS), some of which parallel indices widely used in

animals (e.g., potentiation of the eye blink startle reflex, measured through EMG), the experimenter can also assess feelings of apprehension upon presentation of the CS, through verbal report (Lipp, 2006).

This basic procedure is an important paradigm for the behavioural and cognitive (neuro)sciences. Arguably, much of what we know today about fear, about learning and memory generally, as well as about fear learning specifically, is the result of research that has in some way applied the basic fear conditioning paradigm. It has proven a tool of great use, not only in uncovering the psychological processes that govern the genesis and expression of fear and the functioning of emotional and general memory, but also in exploring the neurobiological underpinnings of emotion and learning (e.g., see Craske et al., 2006; Fanselow and Poulos, 2005; Hartley and Phelps, 2010; Lang et al., 2000; LeDoux, 2000).

Ever since the work by Watson (Watson and Morgan, 1917; Watson and Rayner, 1920), the fear conditioning paradigm is also widely regarded as a prime tool for the experimental study of psychopathology. The idea here is that fear conditioning provides a laboratory model for the pathogenesis of anxiety disorders in the real world (Barlow, 2002; Mineka and Zinbarg, 2006). According to this view, pathological anxiety for stimuli that are essentially innocuous (e.g., house spiders or crowded places) may develop through pairing with aversive events or traumatic experiences (e.g., a frightened mother or a panic attack); such pairing may be experienced first-hand or vicariously. Much like a CS, these originally innocuous stimuli then come to elicit excessive fear or anxiety and spur avoidance behaviour through reference to the associated fearsome event (the analogue of a US).

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The analogy between Pavlovian fear conditioning and the pathogenesis of anxiety disorders has been and continues to be of tremendous heuristic value, for instance in the development of novel techniques to reduce pathological anxiety and to counter relapse after successful treatment (e.g., Culver et al., 2011; Vansteenwegen et al., 2006).¹ However, its merit in inspiring innovations in clinical practice notwithstanding, there is a remarkable paradox in the use of the fear conditioning paradigm as a laboratory model for the pathogenesis of anxiety disorders, conceptually as well as empirically.

Conceptually, Pavlovian fear conditioning is in essence a highly adaptive phenomenon that helps to detect warning signals for impending threats. If a cue in the environment is likely to be followed by something unpleasant, aversive or potentially life-threatening, it is entirely appropriate for an organism to exhibit fear in the face of that cue, particularly if that fear helps him steer clear from the impending danger (Frijda, 1986). In accordance with the adaptive nature of fear conditioning, in laboratory studies mostly everyone will learn to exhibit fear upon confrontation with a cue (CS) that reliably predicts the occurrence of an aversive outcome (US); it is a rather robust and reliable phenomenon.

In clear contrast with the adaptive nature of fear conditioning, pathological fear and anxiety are (by definition) characterized by behaviour that is out of measure with the extent of actual danger-excessive avoidance, exceedingly high levels of subjective fear and anxiety, cognitive preoccupation and the like (Barlow, 2002). And in sharp contrast to people's general susceptibility to fear conditioning, most people confronted with highly aversive, life-threatening or otherwise traumatic situations eventually do not develop an anxiety disorder (Mineka and Zinbarg, 2006). Indeed, up to 95% of people are exposed to one or more traumatic events in their lives, but only between 10 and 30% of trauma survivors develop an anxiety disorder (Engelhard et al., 2008). Clearly, some factors extraneous to the actual experience itself modulate the relation between trauma and anxiety disorder. Research has actually unveiled an array of individual difference factors that are predictive for (and probably causally implicated in) the development of anxiety disorders, ranging from personality traits and dispositions (e.g., neuroticism, trait anxiety, anxiety sensitivity; Gershuny and Sher, 1998; Jorm et al., 2000) over neural indicators (e.g., threat-related amygdala reactivity; Hariri, 2009) to genetic markers (e.g., polymorphisms that affect functioning of the serotonin or dopamine system; Gordon and Hen, 2004; also see Sen et al., 2004). These individual difference factors probably constitute vulnerability factors for reacting maladaptively to significant negative life events in a diathesis-stress model of psychopathology (e.g., Zvolensky et al., 2005).

If such a diathesis-stress model of anxiety disorders is to be reconciled with the idea that fear conditioning plays a crucial role in the etiology of these disorders, one should expect to find differences in sensitivity or proneness to fear conditioning between more and less vulnerable individuals (such differences would in fact represent a main mechanism of vulnerability). Studies comparing clinical and non-clinical populations provide some support for this idea. For instance, anxiety patients exhibit stronger conditioning to the CS+ than healthy controls in a single-cue conditioning procedure (Lissek et al., 2005). In a differential fear conditioning procedure, panic disorder patients compared to healthy controls sometimes

exhibit elevated responding to the CS that is not paired with the outcome (the CS-), resulting in impaired discrimination learning (Lissek et al., 2009). Similarly, panic disorder and post-traumatic stress disorder patients have been shown to be impaired in the extinction of conditioned fear relative to normal controls (Bleichert et al., 2007; Michael et al., 2007).

However valuable such studies, they do not allow to decide whether fear conditioning anomalies represent a true vulnerability factor (i.e., a diathesis) or a diagnostic marker (a consequence) of fear pathology. Despite the putative causal role of fear conditioning in the development of anxiety disorders in a diathesis-stress framework, efforts to relate known vulnerability factors to dysfunctional, excessive fear learning patterns in non-clinical populations have met with much more equivocal results, with most studies failing to find a consistent relationship between factors such as neuroticism or introversion and fear acquisition (e.g., Davidson et al., 1964; Guimaraes et al., 1991; Otto et al., 2007; Pineles et al., 2009) and one recent study even suggesting that high trait anxiety is associated with superior discrimination learning (Indovina et al., 2011).

So here is the empirical paradox: In a basic fear conditioning procedure, people who are at risk for the development of some form of anxiety disorder do not seem to behave differently from people who are not, even though fear conditioning is presumed to be a prime pathogenetic pathway towards the development of anxiety disorders in the diathesis-stress model of anxiety.

We should immediately qualify the preceding statement, as there are in fact a few demonstrations of subtle individual differences in fear conditioning that may be relevant to the pathogenesis of psychopathology. One particularly nice example is a recent study by Lonsdorf et al. (2009). They performed a basic differential fear conditioning procedure, in which one cue (a picture of a human face; CS+) was consistently paired with a mild electrocutaneous shock (US), whereas a second cue (a picture of a different human face; CS-) was presented without shock. On the first day of the experiment, acquisition training was conducted. Remarkably, acquisition was obtained only in carriers of the short version of a polymorphism in the 5-HTT gene. This polymorphism, located in the serotonin transporter gene, is implicated in amygdala reactivity and associated with neuroticism, the latter being a known risk factor for anxiety disorders (Sen et al., 2004). The second day, extinction training was conducted. In those participants who demonstrated acquisition, reliable extinction was obtained only in a subsample consisting of carriers of a specific polymorphism (i.e., val allele carriers) of the gene coding for catechol-O-methyltransferase (COMT). This polymorphism makes the enzyme degrade dopamine particularly efficiently and reduces activity in the prefrontal cortex and connected activity in hippocampus and amygdala (Bildner et al., 2004). Absence of the val allele has been associated with negative mood states such as anxiety and depression, as well as with a lack of benefit from exposure therapy in panic disorder patients (Lonsdorf et al., 2010). These data suggest that individual difference factors that predispose for pathological anxiety may indeed modulate fear conditioning processes, lending some support to a diathesis-stress conditioning model.

Yet, exceptions such as the study just described notwithstanding (and a few other ones, e.g., Baas et al., 2008; Craske et al., 2008; Grillon and Ameli, 2001), convincing evidence for a strong link between individual vulnerability factors for anxiety disorders on the one hand and disordered, excessive fear conditioning patterns on the other hand is surprisingly scarce. There thus appears to be a conceptual incongruity between the adaptiveness of fear conditioning and the dysfunctional nature of anxiety pathology that is reflected at least partly in an empirical discrepancy. People who are vulnerable for the development of anxiety disorders, should, according to a Pavlovian conditioning model of pathogenesis, develop conditioned fears more readily or more strongly than

¹ Note however that Wolpe's technique of gradual or systematic desensitization (Wolpe, 1969), which laid the grounds for current exposure treatments for anxiety, was based not so much on an analogy with conditioning (i.e., extinction) but on the principle of emotional response incompatibility (i.e., you cannot be afraid and relaxed at the same time). Wolpe did use conditioning procedures to induce fear in his laboratory cats (Wolpe, 1958).

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