Contents lists available at SciVerse ScienceDirect

Biological Psychology

BIOLOGICAL PSYCHOLOGY

What's wrong with fear conditioning?☆

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ARTICLE INFO

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.

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).

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 (Blechert 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-SHHTR 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 (Bilder 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

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[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).

others; yet, they do not seem to. Obviously, this state of affairs raises the question whether fear conditioning is such a good model for the pathogenesis of anxiety disorders after all. Is fear conditioning perhaps a valuable tool for investigating adaptive fear learning and normal learning and memory processes in general, but not suitable for the experimental study of dysfunctional fear learning patterns (that is, patterns of fear learning that differentiate between at-risk and not-at-risk individuals)?

In the remainder, we will argue that the relative lack of evidence for individual differences in fear conditioning relevant for anxiety disorders may not be inherently linked to the paradigm of fear conditioning, but may rather reflect limitations of current procedures used to induce and measure conditioned fear in the lab. Specifically, we will argue for the usefulness (1) of including assessment of fearful action tendencies, (2) of assessing fear using indirect or automatic rather than (or in addition to) controlled measures, and (3) of investigating more complex fear conditioning situations than single-cue or differential fear conditioning. Along the way, we will reflect on the relevance of individual differences in emotional response system coherence for human fear conditioning research.

1. Fear conditioning research disregards a crucial component of fear

According to emotion theory, emotions like fear are defined by a loosely connected conglomerate of responses in three different response systems, i.e., subjective experience (e.g., a state of apprehension), physiological activity (e.g., heart rate acceleration), and overt behaviour or behavioural impulses (e.g., to avoid), each being vital to emotional phenomenology (Frijda, 1986; Gross, 2007; Lang, 1985; Lang et al., 1998). Moreover, according to dimensional views on emotion, emotional states are organized around a few fundamental dimensions. The most commonly assumed dimensions are valence (contrasting states of pleasure with states of displeasure), arousal (sometimes referred to as activation, contrasting states of low and high arousal), and approach–avoidance motivation (contrasting states characterized by a tendency to engage with states characterized by a tendency to withdraw; Mauss and Robinson, 2009). Emotional expressions in the different response systems tend to correlate only weakly over individuals and over time (Mauss et al., 2005). To some extent this lack of correlation simply reflects the less than perfect reliability of our measurements (i.e., simple measurement error). However, part of the divergence is also due to the fact that measurement of activity in the three response systems differently reflects the fundamental dimensions that organize emotional states (Mauss and Robinson, 2009). Subjective experience is particularly sensitive to valence and arousal; physiological measures used in fear conditioning research are mainly sensitive to arousal (e.g., skin conductance; Bradley and Lang, 2000) or to valence, but only at high levels of arousal (e.g., startle potentiation; Lang, 1995). Overt behaviour or action tendencies would mainly reflect the motivational component of emotion. Whilst some emotion theories regard these three components as equally important constituents of emotion (Lang, 1985), some even argue that action tendencies constitute the core of emotions, as the ultimate function of emotion is to exert steering control over behaviour (Frijda, 1986). In this view, emotions are defined as felt action tendencies or action dispositions (Arnold, 1960; Frijda, 1986; Lang, 1995). Similarly, emotional disorders are essentially behavioural dysfunctions: A tendency towards avoidance behaviour is one of the diagnostic criteria for many anxiety disorders (American Psychiatric Association, 2000), and etiological models assume that the tendency to escape or avoid threat (whether successfully translated in overt behaviour or not) elicits, maintains and/or exacerbates phobia (Barlow, 2002; Marks and Nesse, 1994). Studying behavioural tendencies might

therefore be of fundamental importance towards understanding when and how adaptive fear might go awry. Yet human fear conditioning research typically samples either subjective experience (asking for verbal report of fear or US expectancy), physiology (measuring bodily reactions such as changes in skin conductance or potentiation of the startle reflex), or both. It is typically not concerned with action tendencies elicited by conditioned stimuli. To its defence, conditioning research as a field has recently rediscovered avoidance as an important topic of study (e.g., Declercq and De Houwer, 2009; Lovibond et al., in press), but mainly as concerns the operant principles and representational structures that govern escape and avoidance behaviour. The transfer of avoidance tendencies to initially neutral cues in human fear conditioning, as an instantiation of fear itself, has so far not been a topic of much interest. We know of only one exception in the literature (Grillon et al., 2006). In that study, after acquisition participants were allowed to navigate freely in two out of three virtual contexts that were associated with no shocks, predictable shocks, or unpredictable shocks, respectively. Results indicated that participants had a strong preference to navigate into the no-shock context and avoid the context associated with unpredictable shocks. More work along these lines seems timely.

2. Fear conditioning research often assesses cognitive or controlled expressions of conditioned fear rather than automatic or implicit fear expression

The current state of affairs implies that one important component of what it means to be fearful (a disposition to avoid) is not covered in research of conditioned fear. Also, the fact that verbal/cognitive, behavioural, and physiological response systems do not always covary in fear learning has long been recognized (e.g., Hodgson and Rachman, 1974; Mineka, 1979), but implications of this divergence for the understanding of pathological fear are never considered. In fact, when in fear conditioning research multiple indices of fear are included – typically subjective report and one or more physiological measures – this is usually done for reasons of cross-validation; divergence between measurements is often attributed to measurement error (see above). Yet, response system divergence and individual differences therein may be informative for understanding pathological fear. For instance, research has indicated that there is a subgroup of people with high vigilance for threat who report low levels of subjective distress upon confrontation with aversive stimuli, whilst at the same time showing elevated levels of physiological arousal (*repressors*; Derakshan et al., 2007; Weinberger et al., 1979). More generally, vulnerability factors for anxiety disorders such as neuroticism and anxiety sensitivity are known to be associated with an unwillingness or inability for accurate subjective report of negative emotions (Barr et al., 2008; King and Emmons, 1990; Paulhus and Reid, 1991). One implication is that individual differences in emotionality (e.g., fear) may be underestimated if one looks merely at cognitive, controllable expressions of fear. This presumably holds true especially for verbal report of subjective anxiety or arousal, but it is well known that some physiological indices widely used in fear conditioning are rather sensitive to cognitive influence as well (e.g., skin conductance; e.g., Lovibond, 2003; Soeter and Kindt, 2010). It is thus conceivable that (some of the) people who are vulnerable for anxiety disorders actually do develop excessive fear in a fear conditioning procedure, but that this excessive fear is not expressed clearly in many of the indices routinely used in fear conditioning research (i.e., subjective report, skin conductance responding), either because excessive fear is evident most strongly in a dimension that is not captured by these measures (i.e., the avoidant action tendency that is a core part of fear; see above) or because
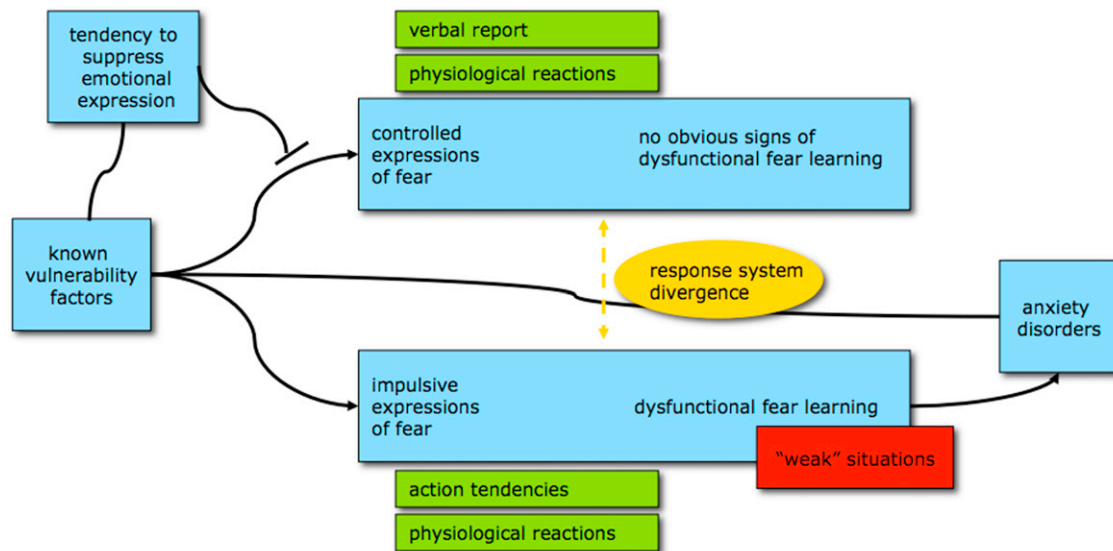
Fig. 1. A working model for the role of fear conditioning in the pathogenesis of anxiety disorders. Excessive fear learning patterns may emerge more easily in implicit expressions of fear (e.g., avoidance tendencies), particularly when confronted with a "weak" fear learning situation. See main text for details.

the measures used are partly sensitive to concealment.[2] As such, psychological dispositions that predispose for anxiety disorders (e.g., neuroticism) may be associated with increased divergence between more and less controlled expressions of fear (e.g., verbal report versus indirect measures; De Houwer, 2006), or between what people (report to) feel and what they do. If so, in some individuals, fear responding may be out of measure with the actual level of threat or more resistant to reduction in some response systems or measures but not in others, resulting for example in excessive fear responses in behavioural expression but not in subjective report (see Fig. 1).

Obviously, much of the above is speculation. It does suggest, however, that it may be important to include in fear conditioning research not only measures that cover all of the fundamental dimensions of fear (valence, arousal, action tendency) but also measures of fear that are relatively indirect and unobtrusive, in addition to more controlled measures such as verbal report of fear or US expectancy. Such measures arguably exist for valence and arousal. For instance, fear conditioning has been shown to endow CSs with the capacity to prime categorization responses in an affective priming task (Hermans et al., 2002). In such a task, clearly positive and negative words are presented on screen, and participants are asked to evaluate these words as quickly as possible. Crucially, the words are preceded by a brief presentation of the CS+ or CS− picture. Reaction time analysis reveals that presentation of the CS+ picture speeds up responding to negative words and slows down responding to positive words, relative to the CS− picture, indicative of an evaluative response to the CS pictures. Importantly, such an affective priming effect is obtained even though CS valence is irrelevant for the task at hand (making it an indirect measure of CS valence). Research suggests that the effect is based on the automatic processing of the valence of the CSs and that it is not dependent upon controlled response strategies (Hermans et al., 2002).

Similarly, startle eye-blink modulation appears to be a relatively uncontrolled index of stimulus valence and arousal, such that arousing stimuli with a negative valence (such as conditioned fear stimuli) potentiate the startle reflex whereas arousing stimuli with a positive valence attenuate the startle reflex (Lang et al., 1990). Research moreover suggests that conditioned stimuli can elicit startle potentiation in the absence of awareness of the CS–US relationship (Hamm and Vaitl, 1996), suggesting that like affective priming, startle potentiation can be considered a relatively uncontrolled measure of fear-conditioned stimulus valence (plus arousal). However, both the selective sensitivity of startle potentiation to negative stimulus valence and the possibility of startle potentiation in the absence of contingency awareness are subject to debate (e.g., Lipp et al., 2003; Purkis and Lipp, 2001).

To supplement such indirect measures with an index that captures specifically the approach–avoidance dimension of fear, we have recently developed a procedure to capture action tendencies induced by fear conditioning. We built on previous work, in which we showed that appetitive conditioning of a CS (i.e., pairing of an initially neutral tray with chocolate consumption) results in the CS eliciting an automatic approach tendency (Van Gucht et al., 2008). After repeatedly pairing the CS+ tray with chocolate consumption (and a CS− tray with no chocolate consumption), participants were presented with pictures of the CS+ or CS− tray on a computer screen. Also on the screen on every trial was a manikin that participants had to move towards or away from the picture as quickly as possible, depending on CS identity. Reaction time data revealed that participants were significantly faster to make the manikin move towards CS+ pictures and away from CS− pictures than vice versa, which indicates that the CS+ picture elicited an automatic tendency to approach that facilitated moving the manikin towards the picture and interfered with moving the manikin away from the pictures (relative to the CS− baseline reaction time speed). We recently modified this procedure in our lab to measure avoidance tendencies towards conditioned fear stimuli. In that procedure, different pictures of one geometrical object (e.g., a cube; CS+) are paired with shock, whereas pictures of a different object (e.g., a cylinder; CS−) are not paired with shock. Afterwards, the pictures are again presented one by one, accompanied by a manikin; participants are instructed to make the manikin move towards or away from the pictures as quickly as possible, based on the orientation of the

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[2] In relation to the former, note that the study by Lonsdorf et al. (2009) that did show different fear conditioning patterns in people at risk for anxiety disorders made use of potentiation of the startle reflex as the index of fear, startle potentiation arguably being a less cognitive index of fear than verbal report or skin conductance (Hamm and Vaitl, 1996; but see Lipp et al., 2003; Purkis and Lipp, 2001; Mallan et al., 2009).

picture. Preliminary results suggest that participants are reliably faster to make the manikin move away from CS+ pictures and towards CS− pictures than vice versa, indicative of a tendency to withdraw from a conditioned fear stimulus (and/or to approach a conditioned safety stimulus, the CS−). Note that the CS pictures elicit that tendency despite the identity of the CS (CS+ or CS− picture) not being relevant for the task (Krypotos et al., in preparation).

The work just described provides merely a proof of principle that fear conditioning results in a conditioned avoidance tendency that can be captured indirectly in a speeded reaction time task. Future work will have to point out whether that conditioned avoidance tendency is particularly sensitive to individual difference variables that are known to be related to disordered anxiety, as hypothesized (e.g., is increased in people with high trait anxiety, more resistant to extinction, or generalizes more broadly).

3. Fear conditioning research samples learning situations that are overly simple and unambiguous

As argued above, basic fear conditioning is essentially an adaptive phenomenon through which an organism learns to anticipate impending threat. Thus, in its simplest form (a CS that is consistently followed by an aversive US), the fear conditioning task represents a "strong situation" (Lissek et al., 2006). A strong situation is one in which the stimuli that are encountered by an individual are unambiguous and predict or constitute a clear hedonistic event. In a strong situation, individuals typically all react with similar, adaptive response patterns. So, applied to the basic fear conditioning procedure, one may expect that the unambiguous threat of an imminent and dangerous stimulus following the CS+ will result in an adaptive fear response to the CS+ that will exhibit limited variability across individuals. Lissek et al. (2006) argue that "weak situations" (situations characterized by ambiguity or uncertainty) provide much more opportunity to reveal meaningful differences in the psychobiology of fear and anxiety (such as differences in fear learning patterns) between patient populations and healthy controls. The same arguably holds for revealing differences within non-clinical populations between individuals with low versus high vulnerability for the development of anxiety pathology. Therefore, even when armoured with indirect measures of fear that are able to capture the avoidance dimension of fear, it is presumably wise to focus on situations that are not overly simple or unambiguous when the aim is to reveal fear learning patterns that may be implicated in the development of anxiety disorders, but to design situations that involve a certain degree of complexity, ambiguity and/or uncertainty. These kinds of situations are abundant in daily life. Indeed, stimuli are typically embedded in a constellation of other discrete stimuli. For instance, the experience of an aversive or traumatic event is typically not accompanied or preceded by a single, clearly predictive signal but surrounded by a variety of cues with different degrees of predictiveness and salience. Under such circumstances, the relation of any one cue in the environment to the traumatic event is clearly ambiguous and various cues can enter into competition for fear-elicitation (i.e., some stimuli can come to elicit fear whereas others do not). One way to model such a situation in the lab is through *cue competition* or selective learning procedures (Fanselow, 1998; Miller and Matute, 1996). An example is a blocking procedure, in which a single CS A (say, a tone) is first paired with a US (e.g., a shock), after which a simultaneous compound of stimulus A and a second stimulus B (say, a flashing light) is also paired with shock. In a normal sample, this procedure may result in high levels of conditioned responding (fear) to A but relatively weak levels of conditioned responding to B, notwithstanding the fact that B has repeatedly been followed by a US (e.g., Lipp et al., 2001). Such blocking of the acquisition

of fear to B has been argued to be highly adaptive, because it implies that an organism learns to fear only those stimuli that are non-redundant predictors of aversive events whilst disregarding redundant ones (Kamin, 1969). However, in reality, the status of B in a blocking procedure is somewhat ambiguous, given that subjects have never experienced the effect of B in itself; if B in itself were also predictive of shock, it would still follow that the joint presentation of A and B could be logically expected to be followed by shock. The fact that blocking relies on an inference about an inherently ambiguous situation is illustrated by the fact that in a normal population, blocking is not always readily obtained (Lipp et al., 2001; Mitchell and Lovibond, 2002); the degree of blocking can be modulated by presenting participants with information that helps resolve the ambiguous nature of the AB compound trials (by informing participants that a compound of two cues that are each individually followed by shock should lead to a stronger shock; Mitchell and Lovibond, 2002; see also Beckers et al., 2006).

Obviously, the ambiguity of a selective learning procedure like blocking constitutes an excellent example of a weak situation. Selectivity in inferences about danger would indeed seem adaptive; a failure to resolve the ambiguity in a selective way (i.e., a tendency to treat all cues that are followed by shock as threat signals, even the redundant ones, and respond to all such cues with fear) would lead to a considerable increase in the number of danger signals in the environment. Such a better-safe-than-sorry strategy would imply that fear and avoidance are provoked by an excessive range of stimuli, including those for which such reactions are not warranted. A recent reanalysis of a few cue competition experiments in our lab provides some evidence that one known vulnerability factor for the development of pathological anxiety, trait anxiety, is indeed associated with a deficit in selective fear learning (Boddez et al., 2012). In these experiments, all participants were presented with a blocking contingency in which one geometrical figure (CS A) was repeatedly paired with shock, after which a compound of that geometrical figure with another figure (CS B) was also paired with shock (A+ then AB+ training). These trials were embedded in a number of filler and control trials. At the final test, participants rated their expectancy of shock for a number of stimuli contained in the experiment, including A and B. Correlational and median-split analyses revealed that the degree of selectivity in fear learning (operationalized here as the level of US expectancy for B) was significantly modulated by participants' level of trait anxiety as indexed by the State-Trait Anxiety Inventory (Spielberger, 1983). Importantly, trait anxiety did not correlate with fear learning for A or any of the other cues included in the design, suggesting that trait anxiety did not affect fear learning per se but specifically the selectivity of fear learning.

Again, these data provide little more than initial evidence for the idea that a lack of selective fear learning in situations of ambiguity may be implicated in the pathogenesis of anxiety disorders. They do suggest that it may be worthwhile to turn to situations that do more justice to the complexity of real-life situations when trying to unravel whether and how at-risk individuals exhibit dysfunctional fear learning patterns. Such situations do not have to be limited to initial fear learning; selective learning or a lack thereof may also have an impact on efforts to reduce fear through extinction or exposure procedures. Suppose that in a blocking-type procedure, one first learns to selectively fear stimulus A (the blocking stimulus) but not stimulus B (the blocked stimulus). From fear conditioning studies in animals (Blaisdell et al., 1999) and causal learning studies in humans (Boddez et al., 2011), it appears that subsequent extinction training of A may unlock the previously blocked fear for B (although no research has yet demonstrated this effect in human fear learning). Such a fear relocation situation may again represent a prime opportunity for individual differences; perhaps at-risk individuals

would be particularly likely to reconsider the inferred safety of B (to the extent that they inferred safety to begin with; see above).[3]

Obviously, a lack of selectivity of fear learning may not be equally prominent in all response systems; arguably, indices of fear that are highly sensitive to voluntary control can be considered particularly prone to overgeneral or non-selective fear learning. Again this implies that individuals at risk for developing patholog-ical anxiety would be characterized by increased response system divergence in selective learning situations, relative to low risk indi-viduals (see Fig. 1).

4. Conclusion

There appears to be a tension between the adaptive nature of fear conditioning and the dysfunctional nature of anxiety disor-ders. Still, we have argued that the fear conditioning paradigm can be retained as a tool for the experimental study of the pathogenesis of anxiety disorders, provided we work with a richer conceptual-ization of fear conditioning than is usually done. This entails that we carefully design situations in the laboratory with a potential for excessive fear learning patterns to emerge (so-called "weak situa-tions"; Lissek et al., 2006) and pay attention to divergence between response systems in these learning situations, particularly minding automatic conditioned responses such as conditioned avoidance tendencies. We have begun work along these lines to investigate whether individuals differences in fear learning patterns can be obtained that are relevant for the understanding of the pathogene-sis of anxiety disorders. We are hopeful that this work will serve to consolidate the diathesis-stress conditioning model of pathological anxiety.

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[3] Unlike the study by Lonsdorf et al. (2009), the few studies that have obtained evidence in non-clinical groups for modulation of fear conditioning by vulnerabil-ity factors employed mostly rather complex designs, such as conditioned inhibition (e.g., Grillon and Ameli, 2001) or contextual fear learning procedures (e.g., Baas et al., 2008). Although these procedures do not represent selective learning situa-tions, they can clearly be considered "weak" (ambiguous or unpredictable) learning situations, fitting with our proposal.

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