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The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders

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Abstract

Current etiological models of anxiety disorders emphasize both internal diatheses, or risk factors, and external stressors as important in the development and maintenance of clinical anxiety. Although considerable evidence suggests personality, genetic, and environmental variables are important to these diathesis–stress interactions, this general approach could be greatly enriched by incorporating recent developments in experimental research on fear and anxiety learning. In this article, we attempt to integrate the experimental literature on fear/anxiety learning and the psychopathology literature on clinical anxiety, identify areas of inconsistency, and recommend directions for future research. First, we provide an overview of contemporary models of anxiety disorders involving fear/anxiety learning. Next, we review the literature on individual differences in associative learning among anxious and non-anxious individuals. We also examine additional possible sources of individual differences in the learning of both fear and anxiety, and indicate where possible parallels may be drawn. Finally, we discuss recent developments in basic experimental research on fear conditioning and anxiety, with particular attention to research on contextual learning, and indicate the relevance of these findings to anxiety disorders.

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1. Introduction

Current etiological models of many mental disorders emphasize the importance of regarding psychopathology as the product of both internal diatheses that confer vulnerability and external (or internal) stressors that further increase the likelihood of developing particular disorders. This conceptualization recognizes the need for understanding individual differences among people that serve as vulnerability factors (such as dispositional traits, or early experiential differences), as well as a variety of environmental stressors that people are exposed to (such as stressful life events or perturbations of the neurochemical environment), and any potential interactions between the two. In the area of clinical anxiety, considerable research is accumulating to suggest certain personality, genetic, and early learning experiences as important diatheses. More proximal stressors often interact with these diatheses and culminate in the onset of a certain disorder. For instance, personality traits such as high trait anxiety or behavioral inhibition appear to be significant diatheses for a variety of anxiety disorders, and early aversive learning experiences have also been found to be important risk factors for the development of these disorders. More proximal adverse circumstances such as exposure to unpredictable and uncontrollable stress, or more discrete conditioning experiences, have been found to serve as stressors in this diathesis–stress framework.

Somewhat less attention, however, has been focused on the *mechanisms* of the putative diathesis–stress interactions

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central in the development of the anxiety disorders. Experimental research on fear learning in animals and humans, although largely a distinct research tradition from psychopathology and individual differences research, is highly relevant for understanding such mechanisms. Individual differences in the ability to learn about various aspects of the environment, combined with actual environmental differences provide parsimonious explanations for how diathesis–stress models may operate with the anxiety disorders. Unfortunately, the gap between the rich experimental literature on fear learning and the growing literature on individual differences as vulnerability factors has prevented an appreciation of these areas as complementary approaches. In this article, we attempt to integrate these two traditions and identify possible areas of inconsistency. We also recommend future directions for research to further explore this diathesis–stress perspective on anxiety disorders.

2. Overview of contemporary learning theory models of anxiety disorders

Pavlovian or classical conditioning was first implicated in the origins of fears and phobias by Watson and Rayner (1920) in their case of Little Albert. The early conditioning models that developed subsequently seemed to assume that traumatic conditioning experiences were both necessary and sufficient for the development of phobic fears and other anxiety disorders. Later as attention gradually came to focus on additional anxiety disorders (such as panic disorder, agoraphobia, and post-traumatic stress disorder), the role of other forms of associative learning in the etiology of this entire category of disorders also began to be examined (e.g., see Mineka, 1985; Mineka & Zinbarg, 1996; Mineka & Zinbarg, 2006). Moreover, many criticisms of the earlier simplistic conditioning views emerged and required careful examination. In this section, we review highlights of the primary themes of contemporary research and thought on learning theory perspectives on five of the primary anxiety disorders.

2.1. Specific and social phobias

Individuals with specific phobias show intense and irrational fears of certain objects or situations, which they usually go to great lengths to avoid. Those with social phobias show excessively high levels of fear of situations in which they believe they might be evaluated by others and they often also go to great lengths to avoid such situations. Problems with early conditioning models of specific and social phobias arose for a number of reasons. First, it became evident that because not all people developing phobic disorders have undergone traumatic conditioning experiences, there must be additional pathways such as vicarious learning to their acquisition (e.g., Rachman, 1978; Rachman, 1990). It also became evident that there are a number of diatheses—both genetic/temperamental and experiential individual differences—which strongly influence the outcome of various kinds of learning experiences and so not all people undergoing the same learning experiences will have the same outcome. Some of these will be discussed below. Thus, direct traumatic conditioning experiences were neither necessary nor sufficient for the development of fears and phobias. Finally, substantial research on the preparedness theory of phobias supported the idea that not all stimuli and situations present during associative learning experiences are equally likely to become the objects of fears and phobias as had originally been maintained by the equipotentiality premise (e.g., Seligman, 1971; Öhman, 1986; Öhman & Mineka, 2001).

2.2. Generalized anxiety disorder

People with generalized anxiety disorder (GAD) show a prolonged pattern of excessive and chronic worry about a number of activities or events in their lives, and experience their worry as difficult to control. Many of the best examples of symptoms resembling generalized anxiety disorder were described by Pavlov (1927) and in the subsequent literature from the 1930s to 1940s on experimental neurosis by Liddell, Masserman, and Gantt. Mineka and Kihlstrom (1978) noted that the pattern of symptoms observed in the numerous experimental inductions of "neurotic" behavior in animals included agitation, hypersensitivity, restlessness, muscular tension and distractibility—all common symptoms of GAD. The symptoms were often apparent outside the experimental situation where the "neurosis" induction occurred and sometimes increased with the passage of time.

Although a myriad of different experimental procedures produced these symptoms, in surveying the literature Mineka and Kihlstrom (1978) concluded that the two most prominent themes common to these procedures were changes in the predictability and controllability of the environment. That is, in all cases important life events that were once predictable and/or controllable became unpredictable, uncontrollable, or both. This led to the idea that perhaps exposure to uncontrollable and unpredictable events was important to the etiology and maintenance of GAD (e.g., Mineka, 1985; Mineka & Zinbarg, 1996; Mineka & Zinbarg, 2006). These ideas are consistent with subsequent experiments in research on learned helplessness demonstrating that exposure to uncontrollable aversive events may be at least as involved in the etiology of anxiety as depression (Barlow, 1988; Barlow, 2002; Mineka & Zinbarg 1996; Mineka & Zinbarg 2006). Furthermore, Seligman and Binik (1977) also demonstrated that exposure to unpredictable aversive events can lead to chronic fear and anxiety because in the absence of signals for aversive events, there are no safety signals telling the person when she/he can relax and feel safe. As such, it is clear that the predictability and controllability of a stressor are important determinants of whether it results in the development of different anxiety disorders. As discussed below, these themes are still relevant to research on fear and anxiety conditioning.

2.3. Panic disorder with and without agoraphobia

People with panic disorder experience recurrent unexpected (and uncued) panic attacks, and they also experience worry or anxiety about having another attack and/or behavioral changes targeted at avoiding another attack. A substantial subset of people who develop panic disorder go on to develop some degree of agoraphobic avoidance of situations in which they perceive a panic attack might occur and from which escape would be difficult or embarrassing. Early learning models of agoraphobia and panic (e.g., Goldstein & Chambless, 1978) were hampered by the lack of recognition of the distinctions between anxiety and panic as partially distinct emotional states at the neurobiological and phenomenological levels. As we understand it today panic disorder is characterized by three distinct phenomena: panic attacks, anticipatory anxiety, and agoraphobic avoidance (e.g., Gorman, Kent, Sullivan, & Coplan, 2000). (See Section 4 for a discussion of these as partially distinct emotional states). Moreover, there was considerable confusion about what constitutes the CS, CR, US and UR in conditioning that occurs during panic attacks (e.g., McNally, 1994).

One current comprehensive learning theory perspective on the etiology of panic disorder avoids these limitations and builds on the growing understanding of these distinctions as well as on advances in the study of classical conditioning. Bouton, Mineka, and Barlow (2001) hypothesized that initial panic attacks become associated with initially neutral internal (interoceptive) and external cues through a conditioning process (e.g., Forsyth & Eifert, 1998). One effect is that *anxiety* becomes conditioned to these CSs and the more intense the panic attack, the more robust the conditioning will be (Forsyth, Eifert, & Canna, 2000). This conditioning of anxiety to both external and internal cues associated with panic sets the stage for the development of two of the three primary components of panic disorder: agoraphobic anxiety and anticipatory anxiety. For example, when people experience their initial panic attacks (replete with strong, often terrifying, internal bodily sensations), conditioning can occur to multiple different kinds of cues ranging from dizziness and heart palpitations to sports arenas or churches. Because anxiety becomes conditioned to these CSs, anxious apprehension about having another attack may develop, as may agoraphobic avoidance of particular contexts.

Bouton et al. (2001) further proposed that *panic attacks* themselves are also likely to be conditioned to certain internal cues. This leads to the occurrence of panic attacks (the third component of panic disorder) that seemingly come out of the blue when people unconsciously experience certain internal bodily sensations (CSs) that can trigger them. Their theory also underscores the existence of diatheses for the disorder, that is, why not everyone who experiences an occasional panic attack goes on to develop panic disorder. Instead, as with phobias, people with certain genetic, temperamental, or experiential vulnerabilities will show stronger conditioning of anxiety and/or panic than others.

2.4. Post-traumatic stress disorder (PTSD)

People with PTSD show heightened arousal, frequent re-experiencing symptoms such as flashbacks and nightmares, emotional numbing, and avoidance of reminders of trauma. Although experiencing a highly traumatic event is a necessary criterion to obtain the diagnosis, it is by no means sufficient because many other individuals experiencing the same trauma do not develop PTSD. Instead, as with the other anxiety disorders, a variety of genetic, temperamental and experiential diatheses interact to determine which individuals are at greater risk for developing the disorder. A number of theorists have argued that the literature on unpredictable and uncontrollable aversive events has great relevance for understanding which individuals undergoing severe trauma will develop PTSD (e.g., Basoglu & Mineka, 1992; Foa, Zinbarg, & Olasov-Rothbaum, 1992; Mineka & Zinbarg, 1996; Mineka & Zinbarg, 2006). First, research on animals has shown that exposure to uncontrollable and unpredictable shock (or defeats in physical fighting) produces many symptoms that resemble those seen in humans with PTSD experiencing similar traumas such as torture, child abuse, and assault. Such symptoms that are shared by animals exposed to uncontrollable stress and humans with PTSD include heightened anxiety and arousal, heightened passive avoidance behavior, and opioid-mediated analgesia that may be related to emotional numbing symptoms (e.g., Baratta et al., 2007; Mineka, Cook, & Miller, 1984; Pitman, Van der Kolk, Orr, & Greenberg, 1990; Rush, Mineka, & Suomi, 1982). Finally, the re-experiencing symptoms of PTSD can be seen as conditioned emotional responses elicited by reminder cues (CSs for trauma) (Foa et al., 1992).

Moreover, Basoglu and Mineka (1992) argued for the relevance of animal research on variables that individuals differ on before, during, and following trauma which have a strong impact on the outcome of exposure to uncontrollable stress. For example, prior exposure to controllable versus uncontrollable stress prior to an index traumatic event strongly impacts the outcome of that traumatic event. Previous experience with controllable trauma seems to immunize against some of the deleterious effects of later exposure to uncontrollable stress (e.g., Baratta et al., 2007; Basoglu et al., 1997; Williams & Maier, 1977). In this sense, such experience with controllable trauma may be a protective factor for PTSD. Conversely, previous experience with uncontrollable trauma can sensitize the individual to the effects of an index traumatic event (e.g., Baratta et al., 2007; Ozer, Best, Lipsey, & Weiss, 2003; Rau, DeCola, & Fanselow, 2005).

In addition, during an index trauma itself, the degree to which it is perceived as uncontrollable can impact the outcome. Stressors that produce a sense of helplessness and defeat lead to higher levels of stress symptoms than stressors which do not produce the same degree of helplessness and defeat (e.g., Basoglu, Livanou, & Crnobaric, 2007; Ehlers, Maercker, & Boos, 2000; Weiss, Glazer, & Pohorecky,

1976; see Mineka & Zinbarg, 2006, for a review). Finally, the course of symptoms following an index traumatic event(s) is affected by subsequent events that ensue. In rats, repeated exposure to the context in which uncontrollable stress has occurred can prolong at least some of the effects of the uncontrollable stress (e.g., Maier, 2001). Similarly, in humans those who have more re-experiencing symptoms following a trauma (functionally similar to re-exposure to the context) are more likely to develop full-blown PTSD than those with fewer re-experiencing symptoms (e.g., Ehlers, Mayou, & Bryant, 1998).

2.5. Summary

This brief overview should illustrate that contemporary learning models involve multiple kinds of learning (not just simple Pavlovian conditioning) such as social learning, vicarious learning, the effects of unpredictable and uncontrollable stress, etc. Moreover, these contemporary learning models of the development of these disorders can easily be interpreted within the context of a diathesis–stress perspective. We now turn to the topic of individual differences in associative learning processes.

3. Individual differences in associative learning processes

3.1. Fear conditioning abnormalities in anxiety disorders

If fear conditioning processes account in part for the development of various anxiety disorders, then relevant individual differences functioning as diatheses should be detectable using classical fear conditioning paradigms measuring the degree and speed of fear acquisition (ACQ) and extinction (EXT). The possibility of individual differences in ACQ and EXT has been explored in both psychophysiological experiments comparing anxious and non-anxious individuals, and has begun to be investigated in behavioral genetic studies. What would be ideal for deepening our understanding of these issues would be longitudinal prospective studies in which individual differences in conditionability of fear or anxiety could be used to predict which individuals would subsequently develop anxiety disorders following relevant learning experiences. Unfortunately, we are not aware of any such studies to date and so we will review highlights of the studies that do exist on individuals with several kinds of anxiety.

3.1.1. Conditioning paradigms used to study individual differences

Although the specifics of classical conditioning paradigms in humans vary across studies, two basic experimental designs have been employed in studies comparing conditioning in anxious and non-anxious groups (Lissek et al., 2005). In the first simple conditioning procedure participants in both groups are first exposed to several CS-only trials (habituation) and are then subjected to repeated pairings of a neutral stimulus (CS) with an aversive stimulus (US). The resulting conditioned response (CR) is measured following the conditioning trials by measuring the CR to the CS presented alone and comparing it with responding during habituation; between group differences are also examined. However, this simple conditioning paradigm does not provide an ideal test of the amount of associative learning that has occurred because it does not control for possible sensitization effects that may occur, especially when anxious participants know they will experience an unpleasant US (independent of its association with a CS).

In the second type of procedure, a discriminative conditioning paradigm, two CSs are used, one paired with the aversive US (the CS+) and one explicitly unpaired with the aversive US (the CS−) (Iberico et al., 2008). Within-subject comparisons of the degree of responding to the CS+ and CS− allow one to infer whether the two groups differ in developing discriminative responding to the CS+ and CS−. One advantage of such paradigms is that they better control for possible sensitization effects because such effects should accrue as much to a CS− as to a CS+. Another advantage is that such paradigms allow for at least indirect comparisons of inhibitory as well as excitatory conditioning.

Unfortunately, it is not entirely clear what should be the nature of the expected individual differences as a function of anxiety as measured by these two paradigms. A number of possibilities exist. Starting with the consideration of simple conditioning paradigms, it is possible that anxious individuals, relative to non-anxious individuals, would either acquire CRs more rapidly or acquire greater magnitude CRs (to either discrete CSs paired with USs, or to contexts paired with USs). This hypothesis leads to the prediction of greater magnitude CRs to CS+ not only during ACQ, but also potentially in EXT because it is known that stronger associations extinguish more slowly (e.g., Annau & Kamin, 1961). Another possibility, however, is that EXT responding might be affected by anxiety without ACQ responding being affected. In the latter case, even if responding in ACQ did not differ between anxious and non-anxious groups, the processes allowing individuals to extinguish fear associations might be abnormal in individuals with or prone to anxiety disorders, leading to a retardation of extinction in these individuals.

3.1.2. Theories about individual differences in conditioning

Another level of complexity is introduced regarding what to predict when we turn to consideration of discriminative conditioning paradigms. However, before considering this issue we first mention several different theories reviewed by Lissek et al. (2005) that were developed to provide an explanation for differences in fear conditioning in anxious versus non-anxious individuals; these are also relevant to predictions about potential group differences in discriminative conditioning.

One theory, advanced by Orr et al. (2000), specifically proposed that individual differences in conditionability to fear stimuli help account for individual differences in

anxiety. This theory predicts that anxious individuals will display stronger or more rapid acquisition of fear CRs than non-anxious individuals, and therefore slower extinction. Specifically, relative to non-anxious individuals, anxious individuals should show increased fear CRs to CS+s as evidenced using a simple conditioning paradigm, and a greater difference in discriminative responding to CS+s and CS−s in a discriminative fear conditioning paradigm. Orr and colleagues argue that these differences could also manifest as slower rates of EXT. For example, GAD patients, compared with non-anxious individuals, showed similar ACQ but reduced EXT of skin-conductance CRs to angry facial expressions (Pitman & Orr, 1986). In addition, using a discriminative conditioning paradigm Orr et al. (2000) found that among trauma-exposed individuals, those who had developed PTSD showed greater discriminative responding both during ACQ and EXT relative to those trauma-exposed individuals who had not developed PTSD. Although they did not use a prospective design, their results are consistent with the possibility that differences in diatheses for the development of PTSD may be a function, at least in part, of differences in conditionability to fear cues.

By contrast, another theory proposed by Davis, Falls, and Gewirtz (2000) identifies a failure to inhibit the fear CR in the presence of safety signals (for example, a CS−, which signals the absence of the aversive US) as one mechanism by which clinical anxiety may develop. This theory is unique in that it specifies differences in inhibitory, rather than excitatory, conditioning, as most relevant to the emergence of anxiety disorders. Some indirect support for this hypothesis in humans comes from a number of studies comparing anxiety patients with controls when they are exposed to a CS−. In some studies, anxiety patients (relative to controls) showed greater fear-potentiated startle during the CS− (Grillon & Ameli, 2001; Grillon & Morgan, 1999) and in others they showed higher magnitude electrodermal responses during the CS− (e.g., Orr et al., 2000). In several other studies, the anxiety patients also showed greater subjective anticipatory anxiety during a CS− (e.g., Hermann, Ziegler, Birbaumer, & Flor, 2002). Results using all three kinds of fear measures thus converge in suggesting that the anxiety patients showed smaller magnitude inhibitory CRs to a CS− than controls. It should be noted, however, that none of these studies provide definitive direct support for hypothesized differences in inhibitory learning as a function of anxiety status because such conclusions require direct assessment of the inhibitory power of the CS− in the two groups and this was not tested in any of these experiments.[1]

[1] One way to assess the inhibitory power of a CS− requires the use of a summation test where the CS− is paired with an independently established CS+ to determine if the magnitude of the CR is reduced relative to when the CS+ is presented alone.

3.1.3. Empirical status of these theories

Lissek et al. (2005) reviewed and conducted a meta-analysis on 20 studies comparing fear conditioning in participants with ($n = 453$) and without anxiety ($n = 455$) (including panic disorder, PTSD, and GAD) to assess the empirical status of these theories. It was found that anxious individuals had stronger fear CRs during ACQ and EXT compared to healthy controls, although both effect sizes were small. Interestingly, these effects were found primarily in studies using a simple conditioning procedure; patients and controls showed similar rates of ACQ and EXT when discriminative conditioning procedures were used. Similar discriminative conditioning in patients and controls suggests that, in addition to stronger excitatory conditioning, anxious individuals may be less able than non-anxious individuals to suppress a fear CR in the presence of safety cues (CS−s). In fact, a number of the reviewed studies using discriminative conditioning paradigms (e.g., Baas et al., 2008; Grillon & Morgan, 1999; Peri, Ben Shakhar, Orr, & Shalev, 2000) found elevated CRs in anxious individuals to both CS+ and CS− stimuli. These findings are not consistent with the Orr et al. (2000) hypothesis (or the Orr et al. results with PTSD) but they are consistent with the Davis et al. (2000) hypothesis that anxious individuals are less able to inhibit fear responding in the presence of safety cues. Again, however, such results are not a direct test of differences in inhibitory learning per se because such a test requires an independent direct assessment of the inhibitory power of the CS− in the two groups rather than simple comparisons of levels of responding to CS− in both groups.

Although a detailed discussion of it is beyond the scope of this article, methodology specifically designed to experimentally distinguish excitatory from inhibitory conditioning has been developed for animals and humans. For example, Myers and Davis (2004) adapted a discriminative conditioning paradigm, originally used for other purposes (Wagner & Rescorla, 1972), called conditioned discrimination, to clearly test the inhibitory power of a CS− in rats. In this paradigm (abbreviated AX+/BX−), the excitatory A and inhibitory B stimuli are conditioned independently of one another, in compound with a third stimulus X. After AX+ and BX− trials, A was excitatory, and B inhibitory. Moreover, one study in human participants with no history of any Axis I disorder also successfully demonstrated the inhibitory effects of B using such a paradigm (Jovanovic, et al. 2005). Using this paradigm, it should then be possible to determine whether individuals with and without anxiety disorders differ in excitatory conditioning, inhibitory conditioning, or both. Other studies are currently underway (Davis, November 2006, personal communication) evaluating this possibility in PTSD.

In addition to the question of whether vulnerability to anxiety disorders reflects individual differences in either excitatory or inhibitory conditioning processes (or both), the question also remains as to whether individual differences in specific-cue versus context conditioning, and fear

versus anxiety conditioning, are relevant to the development of particular anxiety disorders. As will be discussed in the next section, fear learning (as would be evidenced by differential responding to CS+ and CS− in a discriminative conditioning paradigm) appears to be neurobiologically and behaviorally distinguishable from context conditioning (more akin to anxiety), which is the learning of associations between a US and its broader environmental context, rather than specific-cues upon which a US is contingent. If these two processes vary independently, individual differences in either or both may confer risk for specific anxiety disorders.

3.2. Sources of individual differences in fear conditioning: genetic and temperamental differences

If individual differences in either excitatory or inhibitory fear conditioning processes exist, they may be the result of either individual differences in prior learning experiences, or of genetic differences (or both). Although several twin studies of other forms of learning exist, apparently only one study to date has specifically addressed the heritability of fear conditioning. In this study, Hettema, Annas, Neale, Kendler, and Fredrikson (2003) investigated fear conditioning in 173 same-sex twin pairs (90 monozygotic and 83 dizygotic) using a standard discriminative conditioning procedure, pairing either fear-relevant (snakes and spiders) or fear-irrelevant (circles and triangles) pictorial stimuli with a mild electric shock US, measuring skin-conductance (SCR) as the CR. To model the relative contributions of both associative and non-associative processes, habituation as well as acquisition and extinction were assessed. Overall, all components demonstrated moderate heritability, with additive genetic effects accounting for 34–43% of the total variance. Using structural equation modeling, the authors found a two-factor model that best explained the observed genetic variation in twin pairs, one of which accounted for variation in habituation, acquisition, and extinction (the non-associative factor) and one of which accounted for variation in only acquisition and extinction (the associative factor). Interestingly, although statistical power was not sufficient to draw firm conclusions, the investigators also found evidence that the heritability of associative fear learning using evolutionarily-relevant stimuli, such as snakes and spiders, may be greater than that of fear-irrelevant stimuli, such as circles and triangles.

In addition to this one study on the heritability of fear conditioning, there are also a number of stable temperamental and personality factors that are partially heritable which have also been identified as diatheses for various anxiety disorders (Clark, Watson, & Mineka, 1994). One of these is the personality trait known as neuroticism or high negative affectivity and another is trait anxiety—one of several facets of neuroticism. Numerous studies over the years have shown that individuals high in trait anxiety show more rapid and stronger aversive conditioning (e.g., see Levey & Martin, 1981, for an early review; Zinbarg & Mohlman, 1998) and this could be the mechanism through which high trait anxiety operates as a vulnerability factor for clinical anxiety disorders. In this regard it is also interesting to speculate that the partial overlap in heritability of specific phobias and panic disorder (e.g., Kendler, Neale, Kessler, Heath, & Eaves, 1992; Kendler et al., 1995) could be mediated by heritable differences in conditionability (see Bouton et al., 2001). Moreover, research on temperament in children indicates that children with high levels of behavioral inhibition in early childhood are at heightened risk for developing multiple specific phobias in childhood (Biederman et al., 1990), and social anxiety in adolescence when it is most likely to develop (e.g., Hayward, Killen, Kraemer, & Taylor, 1998; Kagan, 1997). Although it is not yet known whether the effects of behavioral inhibition are mediated through differences in conditionability, this seems to be a likely possibility.

3.3. Other sources of individual differences in the learning of phobias and other anxiety disorders

3.3.1. The effects of experiential differences on learning

One major problem with early conditioning models noted by Rachman (1978), Rachman (1990) and discussed in detail by Mineka and Zinbarg (1996), Mineka and Zinbarg (2006) was that although many people who had undergone traumatic experiences developed specific or social fears or phobias, many others did not. For some theorists this seemed to be a critical blow to the conditioning viewpoint. However, Mineka and Zinbarg (Mineka, 1985; Mineka & Zinbarg, 1996; Mineka & Zinbarg, 2006) have long argued that this criticism is based on outmoded and overly simplistic views of conditioning. From the standpoint of contemporary conditioning models such individual differences in the outcome of traumatic experiences (direct and vicarious) are to be expected and one can actually predict the form that they will take.

Examples of individual experiential differences that affect the outcome of aversive learning experiences abound. For example, it is well known that the amount of exposure an individual has had with a potential CS before encountering it in an aversive situation very much affects the outcome of the conditioning experience. This well-known classical conditioning phenomenon is known as *latent inhibition* and illustrates that familiar stimuli or situations result in weaker conditioning than do novel or strange objects or situations (e.g., Lubow, 1998). For example, Kent (1997) showed that children who had had more non-traumatic encounters with a dentist were less likely to develop dental phobia if they were subsequently traumatized by a dentist than were children with fewer prior non-traumatic encounters. Mineka and Cook (1986) also demonstrated a powerful *immunization* effect using a primate model of vicarious fear conditioning to snakes: After observing one non-fearful lab-reared monkey behaving non-fearfully with snakes, otherwise naïve observer monkeys were virtually immune to the robust vicarious fear

conditioning that usually occurs in such naïve observers when they are exposed to a fearful model monkey behaving fearfully with snakes (see Section 3.3.2 for further details).

Similarly, pre-exposure to a US prior to conditioning trials results in reduced acquisition when CS–US pairings occur—the *US-preexposure effect*. That is, familiar USs do not produce as robust conditioning as do novel USs (e.g., Randich & LoLordo, 1979). Moreover, because a history of being reared in *controllable versus uncontrollable environments* appears to affect the amount of fear and anxiety that is experienced by various environmental stressors (e.g., Mineka, Gunnar, & Champoux, 1986), it seems likely that conditioning would be weaker in those reared with a history of control over their environment but this has never been tested directly to the best of our knowledge. However, over a much shorter time-course, one very recent study did indeed demonstrate that rats initially exposed to escapable shocks later showed reduced fear conditioning both to a context and to a discrete CS relative to groups receiving no prior shocks or prior inescapable shocks (Baratta et al., 2007). Conversely, rats initially exposed to inescapable shocks later showed potentiated fear conditioning.

Findings of Basoglu et al. (1997) are also generally consistent with this prediction. They compared rates of PTSD in victims of torture who were later rated as having previously been relatively high versus low on "psychological readiness" for their subsequent experiences with torture. Psychological readiness was measured by a questionnaire asking about the participant's prior knowledge of torture methods, their expectations of being imprisoned and tortured, and their training in stoicism techniques. Those who rated that they had had higher levels of psychological readiness were subsequently less likely to develop PTSD in spite of having received far more torture over a far longer period of time than those who were rated as less psychologically ready. Basoglu et al. argued that the protective effects of readiness were probably mediated at least in part by rendering subsequent torture more predictable, and the stoicism training may also have led the torture to be perceived as partially controllable.

Events that occur *during* a conditioning experience, as well as before it, are also important determinants of the level of fear that is conditioned. For example, the ability to control or escape a traumatic experience reduces the magnitude of the level of fear that is conditioned relative to when the same intensity of trauma is inescapable or uncontrollable (e.g., Mineka & Zinbarg, 1996; Mineka & Zinbarg, 2006; Mineka et al., 1984). Thus, a woman who is attacked by a dog who manages to escape herself would be expected to develop a less intense fear of dogs than a woman who undergoes an identical attack but who does not escape on her own but rather has the dog's owner pull the dog off her. Perceptions of uncontrollability also seem to play a role in social phobia (e.g., Leung & Heimberg, 1996) and animal research has shown that social defeat (an uncontrollable stressor) leads to exaggerated fear conditioned responses (e.g., Williams & Scott, 1989), as well as increased submissiveness to other conspecifics (e.g., Uhrich, 1938) as in social phobia.

In addition, experiences that a person has *following* a conditioning experience may affect the strength of the conditioned fear. For example, the *inflation effect* (e.g., Rescorla, 1974) suggests that a person who acquired a mild fear of driving following a minor crash might be expected to develop a full-blown phobia if she were later physically assaulted, even though no automobile was present during the assault. Even verbal information that later alters one's interpretation of the dangerousness of a previous trauma can inflate the level of fear. These few examples show that the factors involved in the origins and maintenance of fears and phobias are more complex than suggested by earlier simplistic conditioning views, although they are nevertheless consistent with contemporary research and views on learning (Mineka & Zinbarg, 1996; Mineka & Zinbarg, 2006).

3.3.2. Other pathways to the acquisition of fear and anxiety

In addition to these sources of individual differences based on experiential variables, there are at least two other sources of individual differences worth noting. First, as noted earlier not everyone developing phobias or other anxiety disorders seems to have undergone traumatic conditioning experiences. For example, in many instances phobic fears may be acquired vicariously through simply watching another person (live or on a TV or movie screen) behaving fearfully with some object or situation. The strongest evidence for this pathway to the acquisition of fear comes from the primate model of phobic fear acquisition developed by Mineka, Cook and colleagues in the 1980s. They showed that naïve laboratory-reared rhesus monkeys who were not initially afraid of snakes rapidly acquired an intense and long-lasting phobic-like fear of snakes after simply watching a wild-reared model monkey behaving fearfully on some trials when a snake was present and non-fearfully on other trials when a neutral object was present. Many examples of vicarious conditioning of psychophysiological responses (such as electrodermal responses) in humans have also demonstrated vicarious acquisition of aversive conditioning (e.g., Green & Osborne, 1985) and many human anecdotes also corroborate this as an important pathway to the origins of some fears and phobias (specific and social). Although ethical constraints prohibit induction of long-lasting phobic-level fears in human participants, several studies have supported the influence of parental modeling on increasing children's fears at least in the short-term (e.g., Gerull & Rapee, 2002).

With more specific relevance to vicarious learning in social phobias, evidence is accumulating of modeling of social anxiety in families of those who have developed social phobia (e.g., Bruch & Heimberg, 1994; Rapee & Melville, 1997). For example, both socially phobic offspring and their mothers reported more social avoidance in the parents than seen in nonclinical control families. Moreover, in the context of threatening situations parents

of those who develop social phobia often seem to have discussed and thereby reinforced children's avoidant tendencies (e.g., Barrett, Rapee, Dadds, & Ryan, 1996). Related findings have also been observed in panic disorder. Ehlers (1993), for example, found that adults with panic attacks were more likely than controls to have strong learning histories of having been encouraged to engage in sick role behavior when growing up. Similarly, adults with panic attacks were also more likely than controls to report having had chronic illnesses in their households while growing up. That is, observing a lot of physical suffering may contribute to the evaluation of somatic symptoms as dangerous (see also Bouton et al., 2001).

3.3.3. Selective associations in fear learning

Finally, it is also important to mention that some sources of important differences in who acquires phobias and other anxiety disorders do not reside in characteristics or experiences of the person but rather in the nature of the objects or situations that come to be paired with aversive experiences. Contrary to the original equipotentiality premise, humans and primates seem to be evolutionarily prepared to rapidly associate certain kinds of objects or situations—such as snakes, spiders, water, and enclosed spaces—with frightening or unpleasant events (e.g., Öhman, 1986; Öhman & Mineka, 2001). This evolutionarily based preparedness to rapidly associate certain objects or situations that posed real threats to our early ancestors probably occurred because organisms that did so would have enjoyed a selective advantage in the struggle for existence. This stands in comparison with objects or situations that have only come to pose a threat in our relatively recent past (such as guns, bicycles, electric outlets), which are much less likely to become the object of fears and phobias (e.g., Mineka & Öhman, 2002). In the social realm, the kinds of cues that are most likely to become the sources of fears are cues that signal dominance and aggression from conspecifics such as angry or threatening faces (e.g., Öhman & Mineka, 2001).

An extensive line of research in humans conducted by Öhman and his colleagues on human shows that participants develop stronger conditioned responses when slides of snakes, spiders or angry faces, as opposed to flowers and geometric objects or happy faces, are used as conditioned stimuli when paired with mild electric shocks (e.g., Öhman, 1986). Indeed, even very brief subliminal presentations of such prepared stimuli are sufficient to evoke conditioned responses either when presented in acquisition or in extinction. This subliminal activation of responses to phobic stimuli may help to account for the irrationality of phobias because the fear may arise from cognitive structures not under conscious control (e.g., Öhman & Mineka, 2001).

Another series of experiments by Cook and Mineka (1989), Cook and Mineka (1990) showed that monkeys can easily vicariously acquire fears of toy snakes or toy crocodiles but not flowers or toy rabbits. These monkey experiments support the evolutionarily based preparedness hypothesis even more strongly than do the human experiments because the monkeys had no prior exposure to any of these objects prior to conditioning, whereas the human participants in Öhman's experiments may have had preexisting negative associations to snakes or spiders before participating. Thus, if we only had the human studies it would remain possible that ontogenetic factors might play as strong (or stronger) a role as do phylogenetic factors. The monkey experiments are also important because they demonstrate that selective associations occur not only with mild and transient conditioning as seen in the human experiments but also with intense and long-lasting phobic-like fears seen in the monkey experiments.

3.4. Summary

In this section, we have briefly reviewed multiple sources of individual differences in associative learning processes relevant to further our understanding of diathesis–stress perspectives on anxiety disorders. Thus, we discussed how high trait anxiety and clinical anxiety both seem to facilitate acquisition and extinction of conditioned fear using simple conditioning paradigms, whereas discriminative conditioning does not seem to be affected—probably because anxiety is associated with poor inhibitory conditioning. We also reviewed results of one study suggesting that fear conditioning is moderately heritable and that many individual experiential differences occurring before, during, or following fear conditioning trials affect the outcome of those conditioning trials. We also noted that individuals differ in the pathways to acquisition of fear and anxiety—with some being acquired via direct traumatic conditioning and others by vicarious and other forms of learning. Finally, some sources of individual differences reside in the nature of the objects or situations that are associated with aversive consequences rather than in the individuals themselves as seen in research on selective associations.

4. Processes of classical conditioning relevant to anxiety disorders

4.1. Distinctions between fear and anxiety: ethological, clinical, and neurobiological evidence

Historically, the most common way of distinguishing fear and anxiety was whether there is a clear and obvious source of danger that would be regarded as real by most people. When the source of danger is obvious the experienced emotion was called fear, and when one could not specify clearly what the danger was, the emotion was called anxiety. Recently, however, many prominent researchers have proposed more fundamental distinctions between fear and anxiety based on a strong and growing corpus of clinical, ethological, and neurobiological evidence (e.g., Barlow, 1988; Barlow, 2002; Gray & McNaughton, 1996). Although the details across theories vary, there is general

agreement that there are at least two negative emotional states. According to Barlow, for example, fear or panic is a basic emotion involving the activation of the "fight-or-flight" response of the sympathetic nervous system. Anxiety, by contrast, involves a complex blend of negative emotions and cognitions that is both more oriented to the future and much more diffuse than fear. It involves negative mood, worry or anxious apprehension about possible future threat or danger, and a sense of being unable to predict or control the future threat. Physiologically anxiety often creates a state of tension and chronic overarousal but no activation of the fight-or-flight response (e.g., Barlow, 1988; Barlow, 2002). In this section, we outline several of the ways in which fear and anxiety have been distinguished in the human and non-human animal literature and discuss how fear and anxiety are characterized within the context of classical conditioning.

4.1.1. Ethological evidence

From an evolutionary perspective, defensive systems that equip organisms to efficiently and adequately handle a variety of survival threats are of crucial importance for a species. A defensive fear system should motivate the animal to escape or avoid sources of imminent danger with very fast activation of defensive behaviors, but should also be optimized to allow an animal to deal with less explicit or more generalized threat cues without wasted effort or energy. Accordingly, Fanselow and Lester (1988) argued that the defensive fear system in animals is organized such that different behaviors are called forth depending on the animal's psychological (and/or physical) distance from a "predator"—known as "predatory imminence". That is, each type of defensive behavior is designed (i.e., selected through evolution) to prevent movement to the next higher point on the imminence scale.

Specifically, when no threat exists, the animal behaves as usual going about its daily activities. However, when predatory imminence begins to increase, even very slightly, a set of behaviors optimal to the situation is activated. In the rat, for instance, when the predatory imminence is low but non-zero, the animal's meal patterns may change such that the animal shows heightened vigilance, and approach becomes more cautious; according to Fanselow this may correspond to human affective states of anxiety and worry (Quinn & Fanselow, 2006). When a danger (e.g., predator) is actually detected but still at some distance, the animal's heart rate may slow down and respiration becomes shallower as it engages in freezing behavior; this state seems to correspond to the human emotion of fear according to Fanselow. As the threat imminence increases even further and attack is imminent, the animal may jump, return the attack, or flee; this may correspond to human panic attacks. Of critical importance in this argument is that the specific physiological responses and overt behaviors engaged in at different levels of threat imminence differ not just quantitatively, but also qualitatively. In this context, then, fear behaviors are hypothesized to be optimized for moderately imminent threat, and panic behaviors for immediately imminent threat; anxiety behaviors, by contrast, are prompted by less explicit, or more generalized cues, and involve physiological arousal and increased vigilance but often without organized functional behavior. Unfortunately, the underlying neurobiological distinctions between these three sets of responses are not yet fully clarified (Fanselow, November 2006, personal communication).

4.1.2. Clinical evidence

Phenomenological evidence as well as psychometric analyses of clinical symptoms also indicate two relatively independent clusters of symptoms—fear and/or panic symptoms on the one hand, and a more general state of anxious apprehension or worry on the other hand (e.g., Bouton et al., 2001; Brown, Chorpita, & Barlow, 1998; Mineka, Watson, & Clark, 1998). For example, factor analyses and structural equation modeling have uncovered two different factors when examining symptoms of panic, anxiety, and depression in clinical populations. One is exemplified by the kinds of apprehension and worry that are characteristic of anxiety and the other is exemplified by a sense of extreme fear or terror, strong autonomic arousal, and fight-or-flight action tendencies that are characteristic of panic or fear. The anxiety factor (closely related to GAD) is also very closely related to depression. Interestingly, the autonomic arousal symptoms of panic are inhibited in individuals with GAD, suggesting that worry functions to actually suppress heightened autonomic reactivity in this disorder (e.g., Borkovec, Alcaine, & Behar, 2004; Brown et al., 1998). On the other hand, there is also evidence from studies on panic-disordered individuals that panic attacks are actually potentiated when such an individual has a high level of anxiety (see Bouton et al., 2001, for a review). It is not yet clear how to reconcile such apparently anomalous findings with GAD versus panic disorder.

4.1.3. Neuroanatomical evidence

Behavioral neuroscience research in non-human animals also supports the hypothesis of two distinct aversive motivational systems involved in conditioning, although not all researchers agree on the details. For example, according to Davis and colleagues (e.g., Davis & Shi, 1999; Davis, Walker, & Yee, 1997), fear is a short-term state activated by discrete Pavlovian CSs, whereas anxiety is a long-term state that is activated by more diffuse cues that are sometimes unconditioned cues (such as darkness). These states appear to be related to two distinct neural systems, namely, the *amygdala* and the *bed nucleus of the stria terminalis* (BNST), which is immediately downstream from the basolateral amygdala. Although the amygdala mediates fear responses to explicit threatening stimuli, both the amygdala and the BNST are associated with more long-lasting aversive states not clearly linked to explicit threat cues.

Both conditioned and unconditioned fear and anxiety states have been modeled in research on animals, and in many cases these experimental paradigms have been

extended to research in humans. The principal experimental model of conditioned fear has been the *fear-potentiated startle effect*, which is used in both animals and humans. This effect occurs when a greater magnitude startle reflex is elicited by a loud noise occurring 3–4 s after an independently established light CS+ has been presented, compared to when the light is a novel stimulus. The *light-enhanced startle effect*, on the other hand, occurs when a bright light (a mild US for anxiety in rats that prefer the dark) has been turned on 5–20 min prior to a loud noise; this also results in increased magnitude of the startle reflex in rats (Walker & Davis, 1997). The light-enhanced effect in rats appears to be an unconditioned anxiety effect, because it does not extinguish as a source of increased startle either within or across multiple test sessions (Walker & Davis, 1997). In humans, a similar increase in startle amplitude can be induced by exposure to the dark (Grillon, Pellowski, Merikangas, & Davis, 1997). What is common to these two paradigms is that both the longer duration light stimulus (a mild US) and the brief presentation of the light CS+ used in fear-potentiated startle paradigms produce enhanced startle responses.

Using the fear-potentiated startle task, it has been found that the lesions of the basolateral amygdala reduce or abolish behavioral and autonomic responses to conditioned fear stimuli (e.g., LeDoux, 1996). However, such lesions do not reduce a rat's preference for covered arms in a plus maze, a commonly used measure of unconditioned anxiety in animal research (Treit, Pesold, & Rotzinger, 1993). In addition, the lesions of the central nucleus of the amygdala do not reduce the light-enhanced startle reflex—one measure of unconditioned anxiety (Davis et al., 1997). Conversely, the lesions of the BNST have no effect on the fear-potentiated startle effect but do significantly reduce light-enhanced startle reflexes.

It appears that anxiety, in addition to being an unconditioned response to certain situations, can also be learned and evoked by long-duration CSs. For instance, Waddell, Morris, and Bouton (2006) compared the effects of BNST lesions on aversive conditioning with short (e.g., a 60 s noise CS) or long (e.g., a 600 s noise CS) signals for shock. Prior to conditioning, some of the animals received excitotoxic lesions of the BNST, while others received sham lesions. Aversive conditioning was measured via a traditional conditioned suppression task. For the short duration CS, the BNST had no effect on conditioning (of fear), but for the long-duration CS, the BNST lesion significantly reduced conditioning (of anxiety). Therefore, it appears that the BNST is not only involved in the expression of anxiety as is demonstrated by the light-induced startle-effects, but is also involved in the conditioning of anxious apprehension.

4.2. Contextual control of CRs

Conditioned anxiety effects have not only been observed with long-duration CSs as described above but also with contextual cues (Baas et al., 2008; Iberico et al., 2008). It has long been known that when unsignaled shocks are presented to rats in a distinctive environment that the environment itself acquires the capacity to elicit conditioned anxiety. Such contextual conditioning is noteworthy for several reasons. First, reinstatement of fear following full or partial extinction may play an important role in the fluctuating course of symptoms often seen in anxiety disorders (e.g., Bouton et al., 2001; Mineka & Zinbarg, 1996). It is now thought that contextual conditioning plays a critical role in this reinstatement of fear phenomenon seen following the extinction of a CS+ when the US is presented alone. Reinstatement was first described by Rescorla and Heth (1975), who showed that rats whose fear of a CS had been extinguished showed reinstatement of that fear after one or a few exposures to the US alone (not paired with the CS). However, subsequent work showed that reinstatement only occurs if the US is presented in the context where testing for reinstatement is to be conducted (but not if presented in a different context) (e.g., Bouton, 1984). Bouton and colleagues have argued persuasively based on numerous experiments that when the reinstating US is presented, the animal associates it with the current context and the presence of that contextual danger when the CS is next presented triggers fear of the previously extinguished CS. Moreover, recent evidence from Bouton's lab has also confirmed the prediction that lesions of the BNST significantly attenuate reinstatement of fear, presumably because they blocked or reduced context conditioning that would ordinarily occur with the reinstating US (e.g., Waddell et al., 2006).

A second reason that contextual conditioning is important stems from the demonstrations that patients with certain anxiety disorders such as PTSD and panic disorder show elevated *contextual modulation of baseline startle* in experiments in which they know a *fear-potentiated startle* paradigm with an explicit threat cue will be included (i.e., including delivery of shock) (e.g., Grillon & Ameli, 2001; Grillon & Morgan, 1999). In interpreting such enhanced contextual modulation effects it is also important to note, by contrast, that there were no group differences when PTSD and non-PTSD groups both knew that no aversive stimuli would be delivered (Grillon, Morgan, Davis, & Southwick, 1998). However, in these same studies anxiety-disordered individuals did not show exaggerated fear responses to explicit cues for imminent threat (as would be evidenced by greater fear-potentiated startle—i.e., phasic fear to explicit cues) relative to controls. Thus, this elevated contextual modulation of startle in anxiety-disordered individuals seems to represent heightened anxiety in contexts in which something threatening may occur, but this is not accompanied by greater fear to more proximal cues for threat (relative to controls). Very similar results have also been observed recently in normal individuals with high levels of neuroticism—a risk factor for many anxiety disorders (cf. Craske et al., submitted for publication). Such results, of course, raise many interesting questions regarding the relative role of fear versus anxiety conditioning in the etiology of these disorders.

4.2.1. Unpredictability and anxiety

As noted earlier unpredictable aversive events have long been known to be more stressful than predictable aversive events and exposure to unpredictability has been hypothesized to play a role in the development of both generalized anxiety disorder (with more minor events) and PTSD (with more severe events). The most widely cited hypothesis offered to explain these effects is the safety signal hypothesis (e.g., Seligman, 1968; Seligman & Binik, 1977). The idea is that when organisms are presented with signaled (predictable) aversive events they not only know when the event will occur (during or following the CS+) but also when the event will not occur (when the CS is not present—a safety signal). Safety signals allow them to relax and feel safe. By contrast, organisms exposed to unpredictable aversive events have no knowledge of when the threatening events will occur, or when they can relax and feel safe, and thus are in a state of chronic anxiety in this context. Early results on this phenomenon in rats used both stress-induced ulceration paradigms (Weiss, 1971) and conditioned suppression paradigms (Seligman, 1968).

Recently, this work has been replicated and extended using other measures of anxiety in both animal and human participants. For example, Grillon, Baas, Lissek, Smith, and Milstein (2004) have modeled this situation in a human laboratory with normal participants who all experienced three conditions: one in which predictable shocks were given, one in which unpredictable shocks were given, and one in which no shocks were given. Results clearly showed that in the unpredictable shock condition participants showed both greater startle magnitude and higher subjective anxiety than in the other two conditions. Other studies by Grillon and colleagues have shown that in some situations what may be most important in determining contextual levels of anxiety is whether aversive stimuli are *perceived to be predictable* rather than whether or not they actually are predictable, with more conditioning to the context when the participants do not detect the CS–US contingency. So, for example, several studies have shown that participants in a discriminative conditioning procedure who failed to become aware of the CS–US contingency showed more contextual conditioning (i.e., potentiation of baseline startle responding in the startle context) than when they were aware of the contingency. In the latter case, they showed enhanced startle to their CS+ rather than more generalized contextual conditioning (Baas et al., 2008; Grillon, 2002; Grillon et al., 2004; Iberico et al., 2008).

Finally, in one ingenious recent experiment by Grillon, Baas, Cornwell, and Johnson (2006) participants were passively exposed to a virtual reality environment with three virtual rooms (one with no shock, one with predictable shocks, and one with unpredictable shocks). Participants later showed potentiated startle in the unpredictable context relative to the other two contexts, presumably because of greater contextual conditioning with the unpredictable shocks. Furthermore, when allowed to freely enter the three different rooms to find monetary rewards, there was a strong preference for the no shock context and avoidance of the unpredictable context.

It is important to note that the experimental paradigms used to model differences between fear and anxiety behaviorally and neuroanatomically do not necessarily measure different behaviors, but measure behavior under different circumstances. For instance, in both the fear-potentiated startle paradigm and the light-enhanced startle paradigm the dependent variable is the magnitude of startle response; what differs between these two experimental approaches is *when* the startle response is assessed. Accordingly, there is no complete agreement in this literature as to whether fear and anxiety are qualitatively distinct states (as is suggested by the ethological and clinical evidence reviewed above), or are similar responses with different time courses that are elicited by different environments. The future clarification of the relationship between fear and anxiety at each of these levels of analysis will be an important step in advancing our theories of psychopathology of anxiety disorders.

5. Summary and directions for future research

In this review, we have tried to accomplish several goals. First, we briefly surveyed contemporary learning models of several of the major anxiety disorders to set the stage for understanding the importance of individual differences in associative learning among anxious and non-anxious individuals, which may function as diatheses for clinical anxiety. This research indicates that small but significant differences do exist in the rate of fear acquisition and extinction between those with and without clinical anxiety, or between those who are high and low in trait anxiety. We also examined additional possible sources of individual differences in fear learning, including genetic and personality/temperamental factors. For example, one behavioral genetic study has been conducted which documents that the speed and the strength of the acquisition and extinction of fear learning is moderately heritable. Further research should evaluate whether this heritable and stable component of fear learning is directly related to individual differences in trait anxiety or not. Other sources of individual differences in fear learning derive from experiential differences present before, during, and following learning which all have powerful influences on the outcome of particular learning experiences.

A number of important distinctions have also been made in the experimental literature regarding the different types of learning that can occur (e.g., vicarious learning) and the effects of different stimulus and environment characteristics on learning (e.g., selective associability of certain fear-relevant or prepared CSs with aversive USs). For instance, Myers and Davis (2004) have made important progress in the experimental dissociation of excitatory from inhibitory fear learning, which holds great promise to elucidate the exact nature of putative individual differences in fear conditioning. Furthermore, in recent years, a central distinction has been made between conditioning of fear and condition-

ing of a more generalized anxiety state. These appear to be two qualitatively distinct types of learning, produced by somewhat different learning conditions, and it is clear that the two types of learning may differ in their importance to different anxiety disorders, which are far from homogenous in nature. The degree to which individual differences in fear conditioning are independent of individual differences in anxiety conditioning has not yet been assessed, but such dissociations could help to account for more nuanced trait differences in vulnerability to specific anxiety disorders. Study of such dissociations could also enlighten our understanding of exactly how these trait-like variables interact with different environmental situations to result in specific anxiety disorders with distinctive characteristics. Furthermore, additional behavior genetics research into the heritability of fear conditioning should also include paradigms designed to test anxiety or contextual conditioning and should use paradigms that allow differentiation of excitatory from inhibitory processes.

It is likely that by taking such finer-grained distinctions into account, research on associative learning processes in fear and anxiety will better model the complexity of anxiety disorders. Ideally, prospective studies aimed at testing the specific predictions of diathesis–stress models of anxiety disorders involving associative learning factors should be conducted. Currently, individual differences observed in fear learning as a function of anxiety have only been found in individuals who already have high trait anxiety or anxiety disorders. If fear/anxiety conditioning is a diathesis for the development of anxiety disorders, then individual differences in fear and anxiety conditioning should predict the future development of clinical anxiety disorders. Future research should also determine whether this same variability in specific fear/anxiety learning processes may help account for the relationship between trait anxiety (or other dispositional factors, such as neuroticism or behavioral inhibition) and vulnerability to anxiety disorders.

References

Annau, Z., & Kamin, L. J. (1961). The conditioned emotional response as a function of US intensity. *Journal of Comparative and Physiological Psychology, 54*, 428–432.

Bass, J. M. P., van Ooijen, L., Goudriaan, A., & Kenemans, J. L. (2008). Failure to condition to a cue is associated with sustained contextual fear. *Acta Psychologica, 127*(3), 581–592.

Baratta, M. V., Christianson, J. P., Gomez, D. M., Zarza, C. M., Amat, J., Masini, C. V., et al. (2007). Controllable versus uncontrollable stressors bi-directionally modulate conditioned but not innate fear. *Neuroscience, 146*, 1495–1503.

Barlow, D. H. (1988). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. New York: Guilford.

Barlow, D. H. (2002). *Anxiety and its disorders: The nature and treatment of anxiety and panic* (2nd ed.). New York: Guilford.

Barrett, P., Rapee, R., Dadds, M., & Ryan, S. (1996). Family enhancement of cognitive style in anxious and aggressive children. *Journal of Abnormal Child Psychology, 24*, 187–203.

Basoglu, M., Livanou, M., & Crnobaric, V. (2007). Torture vs. other cruel, inhuman and degrading treatment: Is the distinction apparent or real? *Archives of General Psychiatry, 64*, 277–285.

Basoglu, M., & Mineka, S. (1992). The role of uncontrollability and unpredictability of stress in the development of post-torture stress symptoms. In M. Basoglu (Ed.), *Torture and its consequences: Current treatment approaches* (pp. 182–225). Cambridge, England: Cambridge University Press.

Basoglu, M., Mineka, S., Paker, M., Aker, T., Livanou, M., & Gök, S. (1997). Psychological preparedness for trauma as a protective factor in survivors of torture. *Psychological Medicine, 27*, 1421–1433.

Biederman, J., Rosenbaum, J., Hirshfeld, D., Farone, S., Bolduc, E., Gersten, M., et al. (1990). Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders. *Archives of General Psychiatry, 47*, 21–26.

Borkovec, T. D., Alcaine, O., & Behar, E. (2004). Avoidance theory of worry and generalized anxiety disorder. In R. G. Heimberg, C. L. Turk, & D. S. Mennin (Eds.), *Generalized anxiety disorder: Advances in research and practice* (pp. 77–108). New York: Guilford.

Bouton, M. E. (1984). Differential control by context in the inflation and reinstatement paradigms. *Journal of Experimental Psychology: Animal Behavior Processes, 10*, 56–74.

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

Brown, T. A., Chorpita, B. F., & Barlow, D. H. (1998). Structural relationships among dimensions of the DSM-IV anxiety and mood disorders and dimensions of negative affect, positive affect, and autonomic arousal. *Journal of Abnormal Psychology, 107*, 179–192.

Bruch, M., & Heimberg, R. (1994). Differences in perceptions of parental and personal characteristics between generalized and nongeneralized social phobics. *Journal of Anxiety Disorders, 8*, 155–168.

Clark, L. A., Watson, D., & Mineka, S. (1994). Temperament and personality in mood and anxiety disorders. *Journal of Abnormal Psychology, 103*, 103–116.

Cook, M., & Mineka, S. (1989). Observational conditioning of fear to fear-relevant versus fear-irrelevant stimuli in rhesus monkeys. *Journal of Abnormal Psychology, 98*, 448–459.

Cook, M., & Mineka, S. (1990). Selective associations in the observational conditioning of fear in monkeys. *Journal of Experimental Psychology: Animal Behavior Processes, 16*, 372–389.

Craske, M., Waters, A., Nazarian, M., Mineka, S., Zinbarg, R., Griffith, J., et al. (submitted for publication). Context and fear potentiated startle: Risk for emotional disorders.

Davis, M., Falls, W. A., & Gewirtz, J. (2000). Neural systems involved in fear inhibition: Extinction and conditioned inhibition. In M. Myslobodsky, & I. Weiner (Eds.), *Contemporary issues in modeling psychopathology* (pp. 113–142).

Davis, M., & Shi, C. (1999). The extended amygdala: Are the central nucleus of the amygdala and the bed nucleus of the stria terminalis differentially involved in fear versus anxiety? *Annals of the New York Academy of Sciences, 877*, 281–291.

Davis, M., Walker, D. L., & Yee, Y. (1997). Roles of the amygdala and bed nucleus of the stria terminalis in fear and anxiety measured with the acoustic startle reflex: Possible relevance to PTSD. *Annals of the New York Academy of Sciences, 821*, 305–331.

Ehlers, A. (1993). Somatic symptoms and panic attacks: A retrospective study of learning experiences. *Behaviour Research and Therapy, 31*, 269–278.

Ehlers, A., Maercker, A., & Boos, A. (2000). Posttraumatic stress disorder following political imprisonment: The role of mental defeat, alienation, and perceived permanent change. *Journal of Abnormal Psychology, 109*, 45–55.

Ehlers, A., Mayou, R., & Bryant, B. (1998). Psychological predictors of chronic posttraumatic stress disorder after motor vehicle accidents. *Journal of Abnormal Psychology, 107*, 508–519.

Fanselow, M. S., & Lester, L. S. (1988). A functional behavioristic approach to aversively motivated behavior: Predatory imminence as a determinant of the topography of defensive behavior. In R. C. Bolles & M. D. Beecher (Eds.), *Evolution and learning* (pp. 185–212). Hillsdale, NJ: Lawrence Erlbaum.

Foa, E., Zinbarg, R., & Olasov-Rothbaum, B. (1992). Uncontrollability and unpredictability in post-traumatic stress disorder: An animal model. *Psychological Bulletin, 112*, 218–238.

Forsyth, J. P., & Eifert, G. H. (1998). Response intensity in content-specific fear conditioning comparing 20% versus 13% CO-2-enriched air as unconditioned stimuli. *Journal of Abnormal Psychology, 107*, 291–304.

Forsyth, J. P., Eifert, G. H., & Canna, M. A. (2000). Evoking analogue subtypes of panic attack in a nonclinical population using carbon dioxide-enriched air. *Behaviour Research and Therapy, 38*, 559–572.

Gerull, F. C., & Rapee, R. M. (2002). Mother knows best: effects of maternal modeling on the acquisition of fear and avoidance behavior in adults and toddlers. *Behaviour Research and Therapy, 40*, 279–287.

Goldstein, A. J., & Chambless, D. L. (1978). A reanalysis of agoraphobia. *Behavior Therapy, 9*, 47–59.

Gorman, J. M., Kent, J. M., Sullivan, G. M., & Coplan, J. D. (2000). Neuroanatomical hypothesis of panic disorder. *American Journal of Psychiatry, 157*, 493–505.

Gray, J. A., & McNaughton, N. (1996). The neuropsychology of anxiety: Reprise. In D. A. Hope (Ed.), *Perspectives on anxiety, panic, and fear. (The 43rd Annual Nebraska Symposium on Motivation)* (pp. 61–134). Lincoln, NE: Nebraska University Press.

Green, G., & Osborne, J. (1985). Does vicarious instigation provide support for observational learning theories? A critical review. *Psychological Bulletin, 38*, 3–17.

Grillon, C. (2002). Startle reactivity and anxiety disorders: Aversive conditioning, context, and neurobiology. *Biological Psychiatry, 52*, 958–975.

Grillon, C., & Ameli, R. (2001). Conditioned inhibition of fear-potentiated startle and skin conductance in humans. *Psychophysiology, 38*, 807–815.

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

Grillon, C., Baas, J. P., Lissek, S., Smith, K., & Milstein, J. (2004). Anxious responses to predictable and unpredictable aversive events. *Behavioral Neuroscience, 118*, 916–924.

Grillon, C., & Morgan, C. A. (1999). Fear potentiated startle conditioning to explicit and contextual cues in Gulf war veterans with posttraumatic stress disorder. *Journal of Abnormal Psychology, 108*, 134–142.

Grillon, C., Morgan, C. A., Davis, M., & Southwick, S. M. (1998). Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. *Biological Psychiatry, 44*, 1027–1036.

Grillon, C., Pellowski, J., Merikangas, K. R., & Davis, M. (1997). Darkness facilitates the acoustic startle reflex in humans. *Biological Psychiatry, 42*, 453–460.

Hayward, C., Killen, J. D., Kraemer, H. C., & Taylor, C. B. (1998). Linking self-reported childhood behavioral inhibition to adolescent social phobia. *Journal of American Academy of Child and Adolescent Psychiatry, 37*, 1308–1316.

Hermann, C., Ziegler, S., Birbaumer, N., & Flor, H. (2002). Psychophysiological and subjective indicators of aversive Pavlovian conditioning in generalized social phobia. *Biological Psychiatry, 52*, 328–337.

Hettema, J. M., Annas, P., Neale, M. C., Kendler, K. S., & Fredrikson, M. (2003). A twin study of the genetics of fear conditioning. *Archives of General Psychiatry, 60*, 702–707.

Iberico, C., Vansteenwegen, D., Vervliet, B., Dirikx, T., Marescau, V., & Hermans, D. (2008). The development of cued versus contextual conditioning in a predictable and an unpredictable human fear conditioning preparation. *Acta Psychologica, 127*(3), 593–600.

Jovanovic, T., Keyes, M., Fiallos, A., Myers, K. M., Davis, M., & Duncam, E. J. (2005). Fear potentiation and inhibition in a human fear-potentiated startle paradigm. *Biological Psychiatry, 57*, 1559–1564.

Kagan, J. (1997). Temperament and the reactions to unfamiliarity. *Child Development, 68*, 139–143.

Kendler, K. S., Neale, M. C., Kessler, R. C., Heath, A. C., & Eaves, L. J. (1992). The genetic epidemiology of phobias in women: The interrelationship of agoraphobia, social phobia, situational phobia, and simple phobia. *Archives of General Psychiatry, 49*, 273–281.

Kendler, K. S., Walters, E. E., Neale, M. C., Kessler, R. C., Heath, A., & Eaves, L. J. (1995). The structure of the genetic and environmental risk factors for six major psychiatric disorders in women: Phobia, generalized anxiety disorder, panic disorder, bulimia, major depression, and alcoholism. *Archives of General Psychiatry, 52*, 374–382.

Kent, G. (1997). Dental phobias. In G. C. Davey (Ed.). *Phobias: A handbook of theory, research and treatment* (pp. 107–127). Chichester, England: Wiley.

LeDoux, J. E. (1996). *The emotional brain: The mysterious underpinnings of emotional life*. New York, NY: Simon & Schuster, Inc.

Leung, A. W., & Heimberg, R. G. (1996). Homework compliance, perceptions of control, and outcome of cognitive-behavioral treatment of social phobia. *Behaviour Research and Therapy, 34*, 423–432.

Levey, A., & Martin, I. (1981). Personality and conditioning. In H. Eysenck (Ed.), *A model for personality* (pp. 123–168). Berlin, West Germany: Springer-Verlag.

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C., et al. (2005). Classical fear conditioning in the anxiety disorders: A meta-analysis. *Behaviour Research and Therapy, 43*, 1391–1424.

Lubow, R. E. (1998). Latent inhibition and behavior pathology: Prophylactic and other possible effects of stimulus preexposure. In W. O'Donohue (Ed.), *Learning and behavior therapy* (pp. 107–121). Needham Heights, MA: Allyn & Bacon.

Maier, S. F. (2001). Exposure to the stressor environment prevents the temporal dissipation of behavioral depression/learned helplessness. *Biological Psychiatry, 49*, 763–773.

McNally, R. J. (1994). *Panic disorder: A critical analysis*. New York: Guilford.

Mineka, S. (1985). Animal models of anxiety-based disorders: Their usefulness and limitations. In J. Maser & A. Tuma (Eds.), *Anxiety and the anxiety disorders* (pp. 199–244). Hillsdale, NJ: Erlbaum.

Mineka, S., Watson, D., & Clark, L. A. (1998). Comorbidity of mood and anxiety disorders. *Annual Review of Psychology, 49*, 377–412.

Mineka, S., & Cook, M. (1986). Immunization against the observational conditioning of snake fear in rhesus monkeys. *Journal of Abnormal Psychology, 95*, 307–318.

Mineka, S., Cook, M., & Miller, S. (1984). Fear conditioned with escapable and inescapable shock: The effects of a feedback stimulus. *Journal of Experimental Psychology: Animal Behavior Processes, 10*, 307–323.

Mineka, S., Gunnar, M., & Champoux, M. (1986). Control and early socioemotional development: Infant rhesus monkeys reared in controllable versus uncontrollable environments. *Child Development, 57*, 1241–1256.

Mineka, S., & Kihlstrom, J. (1978). Unpredictable and uncontrollable aversive events: A new perspective on experimental neurosis. *Journal of Abnormal Psychology, 87*, 256–271.

Mineka, S., & Öhman, A. (2002). Phobias and preparedness: The selective, automatic and encapsulated nature of fear. *Biological Psychiatry, 52*, 927–937.

Mineka, S., & Zinbarg, R. (1996). Conditioning and ethological models of anxiety disorders. *Nebraska Symposium on Motivation, 43*, 135–210.

Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on anxiety disorders: Its not what you thought it was. *American Psychologist, 61*, 10–26.

Myers, K. M., & Davis, M. (2004). AX+, BX− discrimination learning in the fear-potentiated startle paradigm: Possible relevance to inhibitory fear learning in extinction. *Learning and Memory, 11*, 464–475.

Öhman, A. (1986). Face the beast and fear the face: Animal and social fears as prototypes for evolutionary analyses of emotion. *Psychophysiology, 23*, 123–145.

Öhman, A., & Mineka, S. (2001). Fears, phobias, and preparedness: Toward an evolved module of fear learning. *Psychological Review, 108*, 483–522.

Orr, S. P., Metzger, L. J., Lasko, N. B., Macklin, M. L., Peri, T., & Pitman, R. K. (2000). De novo conditioning in trauma-exposed

individuals with and without posttraumatic stress disorder. *Journal of Abnormal Psychology, 109*, 290–298.

Ozer, E., Best, S., Lipsey, T., & Weiss, D. (2003). Predictors of posttraumatic stress disorder and symptoms in adults: A meta-analysis. *Psychological Bulletin, 129*, 52–73.

Pavlov, I. (1927). *Conditioned reflexes*. London: Oxford University Press.

Peri, T., Ben Shakhar, G., Orr, S. P., & Shalev, A. Y. (2000). Psychophysiologic assessment of aversive conditioning in posttraumatic stress disorder. *Biological Psychiatry, 47*, 512–519.

Pitman, R. K., & Orr, S. P. (1986). Test of the conditioning model of neurosis: Differential aversive conditioning of angry and neutral facial expressions in anxiety disorder patients. *Journal of Abnormal Psychology, 95*, 208–213.

Pitman, R., Van der Kolk, B., Orr, S., & Greenberg, M. (1990). Naloxone-reversible analgesia response to combat-related stimuli in posttraumatic stress disorder: A pilot study. *Archives of General Psychiatry, 47*, 541–544.

Quinn, J. J., & Fanselow, M. S. (2006). Defenses and memories: Functional neural circuitry of fear and conditional responding. In M. Craske, D. Hermans, & D. Vansteenwegen (Eds.), *Fear and learning: From basic processes to clinical implications* (pp. 55–74). Washington, DC: APA Books.

Rachman, S. (1978). *Fear and courage*. San Francisco: Freeman.

Rachman, S. (1990). *Fear and courage*. New York: Freeman.

Randich, A., & LoLordo, V. M. (1979). Associative and non-associative theories of the UCS preexposure phenomenon: Implications for Pavlovian conditioning. *Psychological Bulletin, 86*, 523–548.

Rapee, R., & Melville, L. (1997). Recall of family factors on social phobia and panic disorder: Comparison of mother and offspring reports. *Depression and Anxiety, 5*, 7–11.

Rau, V., DeCola, J. P., & Fanselow, M. S. (2005). Stress-induced enhancement of fear learning: An animal model of posttraumatic stress disorder. *Neuroscience and Biobehavioral Reviews, 29*, 1207–1223.

Rescorla, R. (1974). Effect of inflation of the unconditioned stimulus value following conditioning. *Journal of Comparative and Physiological Psychology, 86*, 101–106.

Rescorla, R., & Heth, C. (1975). Reinstatement of fear to an extinguished conditioned stimulus. *Journal of Experimental Psychology: Animal Behavior Processes, 104*, 88–96.

Rush, D. K., Mineka, S., & Suomi, S. J. (1982). The effects of control and lack of control on active and passive avoidance in rhesus monkeys. *Behaviour Research and Therapy, 20*, 135–152.

Seligman, M. E. P. (1968). Chronic fear produced by unpredictable electric shock. *Journal of Comparative and Physiological Psychology, 66*, 402–411.

Seligman, M. E. P. (1971). Phobias and preparedness. *Behavior Therapy, 2*, 307–320.

Seligman, M. E. P., & Binik, Y. (1977). The safety signal hypothesis. In H. Davis & H. M. B. Hurwitz (Eds.), *Operant–Pavlovian interactions* (pp. 165–188). Hillsdale, NJ: Lawrence Erlbaum.

Treit, D., Pesold, C., & Rotzinger, S. (1993). Dissociating the anti-fear effects of septal and amygdaloid lesions using two pharmacologically validated models of rat anxiety. *Behavioral Neuroscience, 107*, 770–785.

Uhrich, J. (1938). The social hierarchy in albino mice. *Journal of Comparative Psychology, 25*, 373–413.

Waddell, J., Morris, R. W., & Bouton, M. E. (2006). Effects of bed nucleus of the stria terminalis lesions on conditioned anxiety: Aversive conditioning with long-duration conditioned stimuli and reinstatement of extinguished fear. *Behavioral Neuroscience, 120*, 324–336.

Wagner, A. R., & Rescorla, R. A. (1972). Inhibition in Pavlovian conditioning: Application of a theory. In R. A. Boakes & M. S. Halliday (Eds.), *Handbook of contemporary learning theories* (pp. 23–64). Hillsdale, NJ: Erlbaum.

Walker, D. L., & Davis, M. (1997). Anxiogenic effects of high illumination levels assessed with the acoustic startle response in rats. *Biological Psychiatry, 42*, 461–471.

Watson, J. B., & Rayner, R. (1920). Conditioned emotional reactions. *Journal of Experimental Psychology, 3*, 1–14.

Weiss, J. M. (1971). Effects of coping behavior in different warning signal conditions on stress pathology in rats. *Journal of Comparative and Physiological Psychology, 77*, 1–13.

Weiss, J. M., Glazer, H. I., & Pohorecky, L. A. (1976). Coping behavior and neurochemical changes: An alternative explanation for the original "learned helplessness" experiments. In A. Serban & A. Kling (Eds.), *Animal models in human psychobiology* (pp. 141–173). New York: Plenum Press.

Williams, J., & Maier, S. (1977). Transsituational immunization and therapy of learned helplessness in the rat. *Journal of Experimental Psychology: Animal Behavior Processes, 3*, 240–252.

Williams, J. L., & Scott, D. K. (1989). Influence of conspecific and predatory stressors and the associated odors on defensive burying and freezing. *Animal Learning and Behavior, 17*, 383–393.

Zinbarg, R., & Mohlman, J. (1998). Individual differences in the acquisition of affectively-valenced associations. *Journal of Personality and Social Psychology, 74*, 1024–1040.