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EXPERT REVIEW

The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm

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Research on avoidance conditioning began in the late 1930s as a way to use laboratory experiments to better understand uncontrollable fear and anxiety. Avoidance was initially conceived of as a two-factor learning process in which fear is first acquired through Pavlovian aversive conditioning (so-called fear conditioning), and then behaviors that reduce the fear aroused by the Pavlovian conditioned stimulus are reinforced through instrumental conditioning. Over the years, criticisms of both the avoidance paradigm and the two-factor fear theory arose. By the mid-1980s, avoidance had fallen out of favor as an experimental model relevant to fear and anxiety. However, recent progress in understanding the neural basis of Pavlovian conditioning has stimulated a new wave of research on avoidance. This new work has fostered new insights into contributions of not only Pavlovian and instrumental learning but also habit learning, to avoidance, and has suggested that the reinforcing event underlying the instrumental phase should be conceived in terms of cellular and molecular events in specific circuits rather than in terms of vague notions of fear reduction. In our approach, defensive reactions (freezing), actions (avoidance) and habits (habitual avoidance) are viewed as being controlled by unique circuits that operate nonconsciously in the control of behavior, and that are distinct from the circuits that give rise to conscious feelings of fear and anxiety. These refinements, we suggest, overcome older criticisms, justifying the value of the new wave of research on avoidance, and offering a fresh perspective on the clinical implications of this work.

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INTRODUCTION

Avoidance is a natural and adaptive response to danger. Animals, including humans, cannot survive without the ability to avoid harm. Nevertheless, avoidance can have detrimental consequences—excessive and/or unnecessary avoidance is a hallmark of anxiety disorders.[1–8] In order to understand this nuanced behavioral phenomenon, researchers in the late 1930s began studying avoidance conditioning in animals.[9–11] The goal of this work was to illuminate the psychological processes underlying human and animal avoidance, as well as to inform ways to ameliorate the troubling consequences of pathological avoidance in people suffering from debilitating anxiety. But by the 1980s, unresolved conceptual debates and inconsistent findings about the underlying neural circuitry prompted researchers to abandon avoidance and turn to simpler Pavlovian conditioning paradigms.[12–14] The result was a wealth of data about the circuits, cells, synapses and molecules underlying so-called Pavlovian fear conditioning.[15–21] But many important questions have gone unanswered about the clinically important topic of avoidance. Fortunately, after several decades of neglect, there are signs of growing interest in avoidance conditioning and its neural underpinnings.[22–30]

In this review we consider the nature of avoidance conditioning and discuss why it fell out of favor as a behavioral paradigm. We argue that progress in understanding the circuitry underlying Pavlovian aversive conditioning has made it possible to revisit the neural basis of avoidance from a fresh perspective. We also argue that key criticisms that plagued the avoidance paradigm were conceptually misguided. The hypothesis that emerges is that avoidance involves three forms of learning—Pavlovian conditioning, action-outcome learning and habit learning, each mediated by a unique neural circuit. We end with a consideration of the clinical implications of the new wave of avoidance research.

WHAT IS AVOIDANCE CONDITIONING?

Avoidance refers to both a behavioral conditioning procedure used in laboratory studies and a coping strategy used by anxious people. Most of this review will focus on the laboratory research on avoidance, with the clinical implications of that research saved for the end.

In a laboratory context, avoidance is defined as a class of conditioning procedures in which subjects learn to minimize or prevent contact with aversive events (typically electric shocks or stimuli associated with them). Under this broad heading, different forms of avoidance are recognized.[25–35] The broadest distinction is between passive and active avoidance. In the passive avoidance procedure (also called inhibitory avoidance), harm is avoided by withholding responses. A rat that has been shocked when it steps off a platform or enters a certain location can avoid shock by withholding those behaviors. The primary focus of this review is active avoidance, where harm is prevented by taking action. There are several forms of active avoidance conditioning. Some involve warning signals (signaled active avoidance) and others do not (unsignaled or Sidman avoidance). Many studies have used the shuttle box signaled active avoidance procedure, in which a

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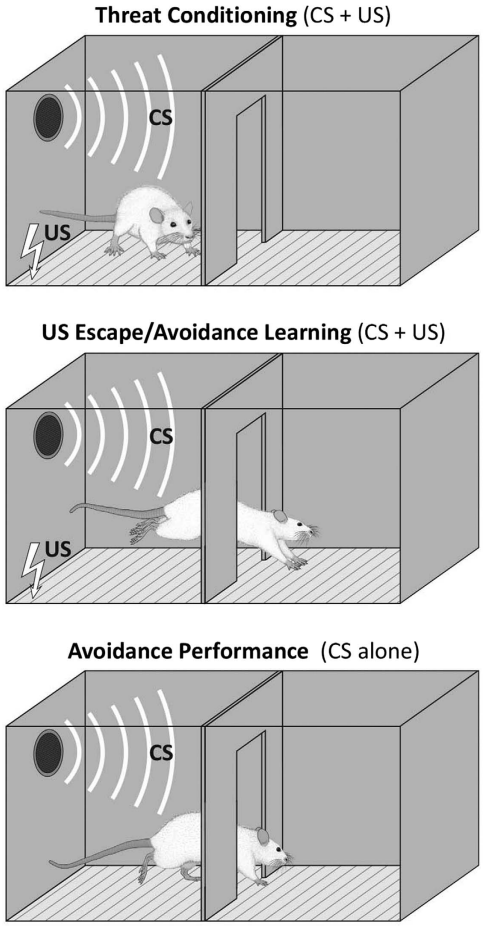

Figure 1. Active avoidance: the shuttlebox learning paradigm. Top panel: initially, subjects undergo Pavlovian threat conditioning, in which a conditioned stimulus (CS; tone) is paired with an aversive unconditioned stimulus (US; shock). Middle panel: once the CS–US association is acquired, subjects learn that the US can be inactivated by shuttling—this is an escape response. On subsequent trials, subjects learn that shuttling during the CS causes the inactivation of the CS and the omission of the US—this is an avoidance response. Bottom panel: once behavior becomes well-trained, the behavior is preformed in the presence of the CS, even though the US does not result. With continued training the behavior persists habitually in spite of the fact that US is no longer predicted by the CS.

warning signal indicates that the subject can avoid harm by crossing a divided chamber (Figure 1). Other signaled active avoidance procedures use responses such as lever pressing or stepping onto a platform to avoid shock. In this review, the term avoidance will refer to active avoidance, except when noted.

THE BIRTH OF THE ACTIVE AVOIDANCE PARADIGM

John Watson[36] built on Ivan Pavlov's conditioning paradigm[37] in founding the behaviorist school of psychology. In one of the earliest and most famous studies of Pavlovian conditioning, Watson presented a young boy with a neutral stimulus (a white rat) in connection with a loud noise.[38] Thereafter, the presence of the rat induced crying and other signs of distress in the boy. This came to be described as 'fear learning,' and paved the way for future studies of so-called Pavlovian 'fear conditioning' in animals and humans. Despite the initial impact of Watson's experiment, much of the research done under the banner of behaviorism focused on the other major form of behavioral learning, instrumental or operant conditioning. In the instrumental conditioning procedure, complex responses are acquired (reinforced) by the outcomes they produce.[39–41] This form of learning was viewed as more relevant to complex human behaviors than Pavlovian conditioning, which involves simpler behavioral and physiological reactions. Coming out of this behaviorist tradition in the late 1930s, O.H. Mowrer[9–11] merged Pavlovian and instrumental approaches by choosing conditioned avoidance for his animal studies of aversion, which he pursued to elucidate the mechanisms of fear and anxiety in humans.

Mowrer accepted on Sigmund Freud's[42] premise that fear and anxiety are learned states, but he recast Freud's ideas in terms of behaviorist stimulus–response principles. According to Mowrer,[9] 'anxiety (fear) is the conditioned form of the pain reaction, which has the highly useful function of motivating and reinforcing behavior that tends to avoid or prevent the recurrence of the pain-producing (unconditioned) stimulus.' Mowrer thought that the Pavlovian conditioned stimulus (CS) served to trigger a fearful state because of its learned association with the aversive unconditioned stimulus (US). If a behavior allowed the subject to remove or minimize exposure to the CS and/or to prevent contact with the US, it was thought to alleviate CS-elicited fear. Thus, Pavlovian conditioning established a CS–fear link, and then through instrumental conditioning a fear-avoidance response link occurs. Behaviors that successfully reduce fear were said to be reinforced and learned for use in the future.[43–49]

Conditioned fear reduction was considered the essential psychological mechanism that reinforced instrumental avoidance behavior.[10,11,45,46,50,51] In this two-factor account of the common avoidance experiment depicted in Figure 1, the rat learns to cross the divided chamber when doing so causes cessation of a tone CS and omission of a shock US. This action, according to two-factor theory, allows the subject to mitigate the fear state triggered by CS. The two-factor theory of avoidance is thus often referred to as two-factor 'fear theory'.[47,52]

Mowrer's ideas and research,[10,11,46,51,53] together with the work of his colleague Neal Miller,[45,50,54] defined laboratory studies of fear and anxiety for the next several decades. A large number of studies were conducted on avoidance behavior[6,31,43,44,49,55–66] and the underlying brain mechanisms.[67–71] Because avoidance was also recognized as a major symptom of pathological fear and anxiety in humans,[72] the Mowrer–Miller approach greatly influenced subsequent ideas about the nature and treatment of these disorders.[1,5,6,52,63,72–75] However, despite the broad impact of the avoidance paradigm, with few exceptions,[76] laboratory research on active avoidance had largely ceased by the mid-1980s.

THE DEATH OF AVOIDANCE

The demise of avoidance research was the result of a number of issues with the paradigm that accumulated between the 1940s and 1980s.[22–24] Particularly troubling were unresolved conceptual debates about the psychological processes underlying avoidance behavior. The arguments carried on for years without coming to a satisfying resolution,[43,44,47,49,52,55–66] causing researchers to question the fundamental value of the paradigm.[60,62] The two most contentious questions were the following: (1) whether fear reduction reinforces the avoidance response; and (2) whether learned avoidance responses qualify as instrumental behaviors under the criteria of learning theory. These questions will be addressed in detail in the next section. For now we consider other issues that had a negative impact on avoidance research.

Interest in the paradigm was also diminished by the fact that no clear picture of the essential neural circuits had emerged, despite years of research.[67–71,77] This was in part due to the poor understanding of neuroanatomical connections in the period between the birth and demise of avoidance. In addition, there was less awareness of how different avoidance tasks might engage different brain circuits. Later research on learning and memory

revealed the strong impact of task structure on the underlying neural circuitry.[78]

Another contributing factor was the success of simple learning procedures used to identify the cellular and molecular substrates of aversive memory in invertebrates.[79,80] This, together with the failure to discover clear neural substrates of avoidance, inspired vertebrate researchers to streamline their approach by adopting simpler experimental procedures, such as Pavlovian conditioning.[13,81–84] A bevy of easy-to-use paradigms for the neuroscientific study of aversive learning and memory were available from behavioral research on Pavlovian conditioning in rodent work that had proceeded in parallel with avoidance research.[48,85–87] Because Pavlovian conditioning is simpler, and thus easier to relate to its brain substrates, a disincentive arose for the use of the more complex and conceptually troubled avoidance paradigm. The net effect was that the field turned to Pavlovian procedures to study aversive conditioning. Over the subsequent decades, Pavlovian aversive conditioning, so-called 'fear conditioning,' emerged as one of the most successful behavioral paradigms for understanding the brain mechanisms of behavior (see discussion of this research below).

Parenthetically, the success of Pavlovian approaches was greatly aided by newly emerging tools that allowed researchers to accurately trace anatomical connections, as well as to uncover the neurochemical constituents of neurons and their synapses.[88,89] Although these methodological developments would surely have aided avoidance research to some extent as well, it is unlikely that avoidance could have succeeded without resolution of the conceptual issues that plagued the paradigm. But, as we will illustrate below, these issues may not be as troubling as they once seemed, especially when they are reconsidered in the light of contemporary ideas about learning and behavior.

DIGGING DEEPER INTO THE CONCEPTUAL STUMBLING BLOCKS

Of the issues mentioned above, most damaging to avoidance research were conceptual problems surrounding the psychological processes underlying the avoidance paradigm. In particular, questions about whether fear reduction reinforces avoidance, and whether avoidance responses are instrumental (that is, learned by their consequences), remained contentious and unresolved, muting interest in avoidance conditioning as a behavioral tool.

Fear reduction as the reinforcer in avoidance

A reinforcer is a stimulus that strengthens behavior, increasing the likelihood that a given behavior will be repeated in similar situations. Negative reinforcement occurs when the elimination of a stimulus makes a behavior more likely to occur again. In the Mowrer–Miller theory, avoidance behavior was said to be negatively reinforced by CS termination because this was hypothesized to reduce the fear state elicited by the CS.[45–47,50,51,53,54]

Despite the early prominence of two-factor fear theory, subsequent empirical work failed to support a role for fear reduction in the avoidance paradigm.[49,57,59,60] One particularly damaging argument against two-factor theory had to do with extinction. Because the avoidance response prevents the US from occurring, presentations of the CS are no longer followed by the US if avoidance behavior occurs on every trial. Put differently, every trial is an extinction trial once avoidance behavior is fully acquired. This should extinguish fear elicited by the CS in and of itself, diminishing the motivation to perform the avoidance response. Yet avoidance persists and is quite resistant to extinction,[6,57,85,90] even though other conditioned responses thought to indicate learned fear (freezing and heart rate)[83,86,91] can be effectively extinguished by withholding an aversive US.[6,85,92,93] Similarly, the behavioral and physiological reactions thought to indicate conditioned fear do not co-vary with the acquisition or performance of the avoidance response.[6,60] Such observations created a paradox for two-factor fear theory. Authors such as Bolles[43,60] and Seligman[62] viewed these observations as particularly damaging to the avoidance paradigm. Two-factor theory fell out of favor in large part due to this disconnect between avoidance behavior and other observable phenomena thought to indicate conditioned fear.

Mowrer's two-factor theory was doomed to controversy by the use of a subjective state (fear) to explain learned changes in animal behavior. Because the relationship between a conscious feeling and a behavior is ultimately unverifiable in rodent subjects, the central tenant of two-factor fear theory cannot be tested in a satisfactory way in animal studies. Even if objective responses thought to indicate conditioned fear in rats did vary with avoidance, the connection between those indicators and a conscious feeling of fear could not be conclusively established. In fact, in humans, behavioral and physiological responses are poorly correlated with subjective states.[7,94,95] If feelings of fear do not correlate with other indicators in humans, why should they in rats? Fear theory was predestined to wind up in an intractable debate, and its early prominence painted avoidance research into a corner.

To solve this problem, some offered an alternative two-factor model, called aversion theory, that did not posit fear reduction as the reinforcer.[55,56] Instead, it simply gave a behaviorist explanation—the Pavlovian CS is aversive, defined by the observable fact that animals will work to remove it. Thus, CS inactivation negatively reinforces avoidance behavior. But the field was committed to some kind of fear-based explanation. The result was an effort to operationally redefine fear as something other than a subjective state, focusing instead on observable stimuli and responses.[39–41] Fear came to be a psychological or physiological intervening variable that accounted for relation between external and defensive behavior.[40,43,47,48,61,63,91,96–105]

Despite such attempts at reformulation, these operational definitions of fear were not used consistently. For some, fear remained a conscious feeling. Mowrer,[10] for example, called for the return of consciousness to studies of animal behavior, arguing that rats freeze 'by-cause of fear.' Contemporary researchers such as Panksepp[106,107] argue that the conscious feeling of fear arises from the same circuits that control defensive behavior in both rats and humans. In this view, as in Mowrer's, freezing in rats should tell us about fearful feelings in people. However, even those who tried to define fear without reference to subjective states would use the term in more than one way. Bolles,[97] for example, called for care in the use of subjective state terms like fear because of the surplus meaning they possess, but also wrote about 'frightened rats.' Bolles' student, and prominent 'fear' researcher, Michael Fanselow says that a goal of science should be to 'replace inaccurate subjective explanations… with more scientifically grounded explanations'.[104] Yet, he and other "fear" reserachers claim that freezing rats can help understand pathological fear (presumably subjectively expereinced fear) in humans.[20,21,102,103,105,108,109] Clearly, confusingly mixed meanings of the term fear were, and still are, in common use.

In an insightful commentary on operational definitions and their monikers, Marx notes that it is important to distinguish operational validity, which concerns the empirical relation between observable variables, and semantic validity, which refers to the relation of the name applied to the operational definition.[110] He points out that there is a 'semantic danger' that results when 'names chosen to represent the intervening variable have …vague and varied meanings.' When common language terms are redefined in novel ways, the result, according to Marx, is that it is not always clear, which meaning is in play because 'each reader tends to read into the word…his own meanings and biases'. Attempts to redefine fear in nonsubjective terms suffer from this problem. For instance, the common meaning of the word fear (for

example, a subjective sense of being in danger) is often conflated with the empirical basis of the operational definition (defensive responses elicited by threatening stimuli). As a result, for some, empirically observed behavioral outcomes are treated as an index of subjective feelings of fear, while for others fear is nothing more than activity in the circuit that connects threats to defense responses. As Marx's analysis predicted, the situation has lead to confusion.

Our position is that subjective states of fear should not be invoked to describe the defensive behavior of species in which such states cannot be verified by verbal report.[30,111,112] While we do not deny the possibility of such states in nonhuman animals, we argue that they cannot be directly assessed in nonverbal species.[30] At the same time, just as problems arise from calling upon subjective fear in animals, so do they arise from failing to acknowledge the role of such states in humans,[104] a species in which they can be verified and studied. Subjective experiences of fear and anxiety are a leading factor that causes people to seek clinical help, and therapies are judged successful largely based on their capacity to change these subjective experiences. This is probably why many researchers, even those who deny that subjective states have value as a scientific topic,[104] feel compelled to refer to nonsubjective meditational states as states of fear or anxiety, and claim relevance to human fear and anxiety.[20,21,102,103,105,108,109]

In order to discuss the processes underlying avoidance without falling prey to the conceptual issues associated with two-factor fear theory, a change in terminology is required. As Bolles once noted, subjective state terms from human experience will always carry surplus meaning.[97] To minimize subjective surplus meaning, we propose that what was once considered a fear stimulus can be referred to as a threat, which we conceive of as a potential source of danger or a danger-predictive cue. Fear conditioning, by the same token, simply becomes Pavlovian threat conditioning (PTC).[112] A fear response becomes a defensive response, which we define as the behavioral outputs that protect against danger and physiological responses that support these responses. Given that numerous investigators use fear response and defense response interchangeably, this should be non-controversial. We can study how threats control these defensive responses (including avoidance) in animals and humans alike, without conflating defensive processes with the mechanisms of conscious fear experiences.[30,111–113] These terminological changes allow us to consider the underlying mechanisms in humans and animals on a level conceptual playing field. If subjective fear does not account for expression of CS-elicited Pavlovian defense responses, reduction of CS-elicited subjective fear cannot be the explanation for the why avoidance is reinforced and learned, or why, once learned, the avoidance responses are performed.

From a neuroscientific perspective, behavioral learning can be accounted for in terms of cellular and molecular events occurring in functional circuits. These events strengthen connections between stimuli in Pavlovian conditioning, and between actions and outcomes in instrumental learning. There is no need to introduce a fear construct. This point is highlighted by the observation that human feelings of fear are poorly correlated with physiological responses that are thought to measure fearful feelings,[7,94,95] and by findings in healthy participants[114–120] and blindsight[124–127] patients showing that threats elicit defensive responses without the person knowing the stimulus is present and without feeling fear. Moreover, amygdala damage in humans disrupts physiological and behavioral responses but not conscious feelings.[121–123] These and related observations lead to the conclusion that different circuits underlie fearful feelings and defensive responses in humans.[30,128]

The term fear will always carry extra meaning when used to name a nonsubjective state that functions as mediator between threats defensive responses. This is true whether we are discussing humans or other animals. Nonconscious fear, in short, is a cumbersome and misleading concept. The mediator between threats and defensive responses is a defensive circuit that involves the amydgala and related brain regions. Although the activity in this circuit does not itself give rise to a conscious fear state, it nevertheless contributes indirectly to the conscious experience of fearful feelings, which, we propose, are products of cortical systems.[30] We therefore prefer terms such as 'defensive motivational circuit' or 'defensive system'[30,49,111,112,129,130] that are less intrinsically biased toward subjective interpretations by their common language meaning.

In summary, conceptual problems with fear reduction can be circumvented by acknowledging that important defensive responses can be accounted for without making reference to conscious experience. In lieu of fear reduction, we take a brain-based approach to defensive behaviors evoked by conditioned threats. Though we have been critical of two-factor fear theory, we do agree that avoidance behavior involves distinct learning processes that occur in sequence. As described below, we propose three learning processes. First, the subject acquires an association between a CS and an aversive US through Pavlovian threat conditioning. Next, we believe that a negative reinforcement process guides the instrumental acquisition of the avoidance response. Third, we argue that the avoidance behavior becomes habitual with significant training, allowing it to persist even when it becomes disconnected from its reinforcing consequences.

Instrumentality of avoidance

An instrumental action is shaped by the outcomes it produces.[131] As noted above, early researchers assumed that avoidance was acquired through instrumental conditioning, but this idea was strongly criticized. Here we re-evaluate the arguments against the role of instrumental learning in the avoidance paradigm. We contend that many of these critiques were flawed in unappreciated ways and should no longer impede contemporary research on avoidance learning.

One criticism of the instrumentality of avoidance was actually a problem with two-factor fear theory itself. The influence of the Mowrer–Miller approach caused fear reduction to become conflated with an instrumental interpretation of avoidance behavior. Much of the field concluded that avoidance could not be considered instrumental without a fear-reduction reinforcement mechanism. Once two-factor theory fell out of favor, the instrumentality of avoidance was also dismissed. An obvious alternative was not given substantial consideration—that the avoidance response is instrumental even though fear alleviation is not the relevant reinforcer. The failure of two-factor fear theory says more about the field's view of fear than about the role of instrumental processes in avoidance behavior.

Another issue revolved around a key control condition, the yoked control, in avoidance research. In this procedure, subjects are paired such that one animal determines the delivery of stimuli for both, creating an arrangement in which both subjects receive the same temporal pattern of experimental events even though only one has control. This design was a major tool used to establish the instrumentality of a behavior. However, the yoked control has been forcefully criticized. In particular, Church argued that within and between subject variation can systematically bias the paradigm, leading to differences in group behavior that are not necessarily due to instrumental control.[132,133] The ambiguities of the yoked design, which had been in common use, made it methodologically difficult to establish the instrumentality of avoidance. This methodological problem added impediments to the question of how to study instrumentality, but this is not the same as evidence against instrumentality.

There were other criticisms, as well. Bolles, for example, argued that avoidance behavior was a CS-controlled, species-specific

defensive response.[59,60,91] Specifically, avoidance was defined as CS-elicited 'flight', acquired through Pavlovian learning. Because flight responses are not modifiable by the consequences they produce, Bolles concluded that avoidance was not instrumental. However, there are fundamental differences between the classic flight response and avoidance. Flight is typically a stereotyped, innate burst of activity in reaction to imminent danger. An avoidance behavior is a complex action that can take a number of forms, which vary substantially between individuals and situations. Often the avoidance responses in a shuttle box more resembles locomotion[134] or 'active wandering'[135] than the rapid burst of activity characteristic of innate flight that Bolles seems to refer to. Moreover, avoidance responses are acquired and maintained in ways that make them distinct from Pavlovian responses. Relative to Pavlovian freezing, avoidance responses are more slowly acquired, more difficult to extinguish, more variable and are mediated by different brain circuits (see below).

Another important point that is not widely recognized is that key findings in the classic literature on avoidance involved data collected from animals that had undergone extensive training.[57,85,90] Modern learning theory recognizes that well-trained responses can become habits, which are actions that continue despite a weakened connection to the reinforcing outcome by which they were first acquired.[131,136–140] This is critical, because a behavior's instrumentality (that is, outcome dependency) cannot be assessed once that behavior has become habitual (that is, outcome independent). The focus on well-learned habitual responses may account for at least part of why past research was unable to establish a role for instrumental conditioning in avoidance.[43,48,49,59,60]

The concept of habit also resolves the extinction paradox described in the previous section. Briefly, if a subject avoids on every trial, it no longer has contact with the aversive US, and the avoidance response should extinguish. Critics wondered why the response persisted in such a situation. Habit provides a conceptual resolution to this problem. Contact with the reinforcing stimulus is not required once a behavior has become habitual.

Habit also sheds light on the inconsistent results of early neuroscientific studies of avoidance.[68–71,76] Appetitive studies have shown that the transition from instrumental action to habit involves a shift in the underlying neural circuitry.[136,139,140] Consistent with the appetitive work, the amygdala is required for the acquisition and expression of the avoidance response,[141] but not for avoidance after extensive training.[142] Amygdala manipulations carried out at different time points thus produce inconsistent results, which were difficult to interpret without acknowledging an important third factor in avoidance learning.

In short, the idea of habit is an important solution to more than one issue with the avoidance paradigm. But why does avoidance become habitual? Habit is a form of 'automatic' behavior that can be acquired with substantial experience. The advantage of automaticity is that it allows the brain to bypass the extensive neural circuitry needed to process environmental contingencies that have already been established. Instead, a streamlined circuit directly connects a stimulus to a response. While this fosters efficient processing, the cost is a reduced sensitivity to changes in outcome. Future research on avoidance should explore the hypothesis that habit is a crucial third factor in avoidance learning.

The arguments against instrumentality have long stigmatized avoidance as being too problematic to pursue. While flaws in key critiques do not establish the instrumentality of the avoidance response, we believe that our re-evaluation of the literature justifies a fresh look at the avoidance paradigm. Moving forward, studies designed to assess the psychological structure of avoidance conditioning will benefit from advances in learning concepts that arose after avoidance work fell out of favor. For example, the notion that actions can become habits is an insight from learning theory that has already paid off. Further, nuanced criteria have emerged to determine if a behavior is instrumental,[136,137,143–150] providing clearer guidelines for pursing the instrumentality of avoidance as the new wave of research proceeds.

REINFORCEMENT OF AVOIDANCE

While more work is needed to establish the instrumentality of avoidance, we can identify possible reinforcers of avoidance behavior. Some potential negative reinforcers include omission of the US (for example, prevention of a shock), escape from the CS (for example, termination of a tone) or escape from the US (for example, omission of a shock). It can be difficult to distinguish between these possibilities using an active avoidance task.[60,151]

The escape from threat (EFT) paradigm, often called escape from fear,[48,151,152] was designed to shed light on potential mechanisms of negative reinforcement. In EFT, rats first undergo Pavlovian conditioning to a tone CS and a shock US. The next day they are placed in a novel chamber where the tone CS is presented. Over trials, subjects will learn to make a specific response, such as shuttling in a runway, in order to inactivate the CS. This response is reinforced completely by tone offset, as the US never occurs in the novel chamber. EFT demonstrates that CS escape is sufficient to reinforce instrumental learning. Although early EFT paradigms were subject to a number of criticisms, many of these were addressed in more recent work[151] and it seems clear that CS termination can act as a negative reinforcer.

Because EFT learning is somewhat weak, avoidance may depend on both escape from the CS and prevention of the US. Indeed, evidence suggests that both CS inactivation and US omission act synergistically to reinforce avoidance responses.[58] Thus, active avoidance behavior is likely negatively reinforced by multiple salient outcomes, each of which contribute to the acquisition and performance of the response. Studies of the brain mechanisms of negative reinforcement should consider these possibilities.

Another possibility is that avoidance is reinforced, not by the removal of danger, but by the addition of safety cues. Stimuli associated with successful avoidance, such as the offset of the CS, may function as conditioned inhibitors—signals that are associated with the absence of shock.[33,153,154] In this sense, avoidance is positively reinforced by the presence of safety cues. An elaboration of this argument suggests that the avoidance response itself functions as a conditioned inhibitor.[155] Because the shock is absent when the CS and the avoidance response occur together, the response becomes a signal that discriminates between trials on which the US will and will not occur. Thus, the action itself becomes associated with the absence of shock via Pavlovian learning, and this association inhibits the usual responses (for example, freezing) evoked by the CS. While this is an intriguing idea, we note that freezing and other Pavlovian responses remain suppressed when the CS is presented in an alternate environment that does not allow the avoidance response.[85,156] In other words, avoidance training can attenuate conditioned aversive behaviors elicited by the CS even when the response is not present.

There is an important sense in which avoidance of danger and approach to safety are necessarily entwined—if safety is the absence of danger, avoidance is a source of safety. Thus, we believe that negative reinforcement resulting from removing threat and positive reinforcement from achieving safety are complimentary processes that may both contribute to avoidance learning, though perhaps in differing degrees.

Mowrer[10] talked about negative reinforcement in terms of fear reduction, leading to 'relief,' and he conceived of approaching safety as the experience of 'hope.' In our view, reinforcement in avoidance, whether negative reinforcement from the reduction or removal of threats or positive reinforcement from the presence of safety signals, involves cellular and molecular processes in the

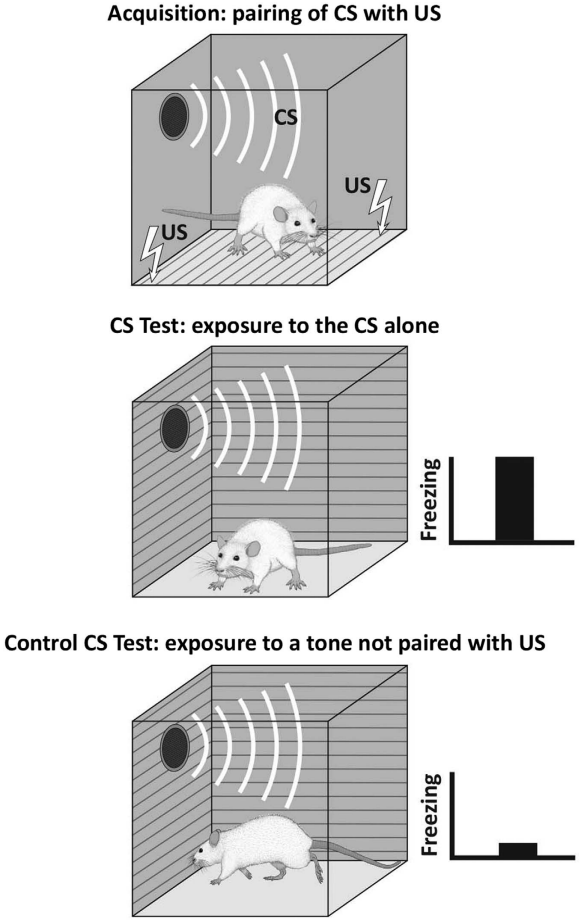

Figure 2. Auditory pavlovian threat conditioning. Top panel: an auditory conditioned stimulus (CS) is paired with a foot shock unconditioned stimulus (US). Middle panel: when the CS is presented in a novel context, it elicits a conditioned reaction, freezing. Bottom panel: if the CS is not paired with the US it does not elicit freezing during the test.

functional circuitry of avoidance. These events provide the necessary and sufficient reinforcement mechanism to account for behavioral learning. Subjective experiences of fear, hope, relief or other emotions may occur but are not the cause of learning.

THE RESURRECTION: REVISITING AVOIDANCE ACTION CIRCUITRY THROUGH THE LENS OF THE PAVLOVIAN REACTION CIRCUITRY

In the previous two sections, we argued for the flaws in the major conceptual stumbling blocks that have hampered avoidance research. As a result, the renewed interest in the avoidance paradigm and its neural underpinnings is justified. In pursuing the neural basis of avoidance, we build on the argument mounted above—that avoidance involves three distinct types of learning, each supporting different behaviors that are acquired sequentially. Initially, Pavlovian conditioning results in defensive reactions, which are stereotyped species-specific behaviors (freezing, for example). These are supplanted by defensive actions (avoidance responses), which are a more flexible class of behavior that, we hypothesize, are learned by their outcomes. Finally, with additional training actions transition into defensive habits, which are highly persistent and outcome insensitive actions (habitual avoidance responses). Below we will demonstrate that these three classes of behavioral learning depend on dissociable neural substrates.

Because Pavlovian conditioning is the first of the three phases, we argue that the wealth of data about the neural circuitry of PTC can be leveraged to more effectively pursue the neural basis of avoidance learning, especially if the avoidance paradigm chosen uses CSs and USs that have been used in the Pavlovian work. For this reason, we focus on a signaled active avoidance paradigm that uses a tone CS and a footshock US. This allows us to ask whether the amygdala-based circuitry underlying Pavlovian defensive reactions overlaps with or diverges from the circuitry required for avoidance. If the circuitry of reaction and action overlap entirely, avoidance is likely to be a wholly Pavlovian process. If the action circuitry diverges from the reaction circuitry, it would suggest that reactions and actions are acquired through at least partially distinct processes. In addition, the substrates of defensive actions can be compared with the well-characterized substrates of appetitive instrumental action, which may inform the form of learning that supports active avoidance behavior. The relationship between action and habit can be evaluated similarly.

Neural circuits underlying Pavlovian threat conditioning

As noted above, PTC occurs when a neutral CS (for example, tone) is paired with an aversive US (for example, footshock) (Figure 2). The amygdala is a critical substrate of PTC in both humans and animals.[16,157–160] Rodent studies demonstrate that the CS and US converge in the lateral nucleus of the amygdala (LA).[161–163] During conditioning, LA neurons exhibit increases in neuronal activity evoked by the CS.[164–169] This activity is necessary to support learning—destruction or inactivation of LA disrupts both the acquisition and expression of Pavlovian reactions.[170–172] Within LA a variety of cellular and molecular events transform a neutral stimulus it into an aversive CS.[16,18,160,173–175]

LA projects to a variety of other nuclei within the amygdala.[176–178] Of critical importance for PTC is the progression of information from LA to the central nucleus of the amygdala (CeA). Similar to LA, CeA contributes to the acquisition of PTC,[179–183] which depends in part on the potentiation of LA synapses in the lateral subdivision of CeA.[184] However, CeA is best known as a major amygdalar output nucleus that controls the behavioral, autonomic and endocrine reactions elicited by the CS.[83,185,186] Projections from CeA to the periaqueductal gray (PAG) are necessary for CS-evoked freezing,[185,187] while projections to other hypothalamic and brainstem targets control autonomic and neuroendocrine reactions to the CS.[83,185]

It is important to note that the connections between LA and CeA are both direct and indirect. The indirect connections involve LA projections to basal amygdala (BA), medial amygdala and the intercalated nuclei—each of which projects to CeA.[176–178] Information about conditioned threats may travel through one or more of these pathways in order to engage the appropriate conditioned defensive reaction.

While the human amygdala cannot be explored in such detail, studies of patient populations, as well as brain imagining studies of healthy participants, confirm the basic findings of animal research. Damage to the human amygdala disrupts PTC,[188,189] and PTC elicits BOLD activity in the amygdala of healthy participants.[190–192] Recent studies using depth electrodes support a role for the human LA in the rapid processing of aversive stimuli.[118,193] The human amygdala supports implicit or nonconscious forms of threat processing,[30,100,112–120,123] which can be assessed explored similarly in humans and other mammals. The rodent amygdala is an apt model for nonconscious amygdala-dependent threat processing in humans.

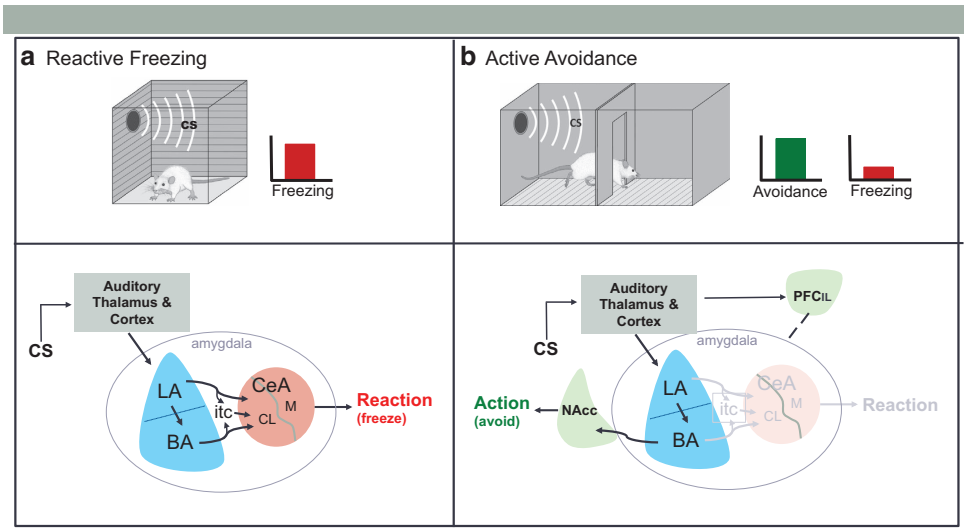

Figure 3. Neural circuits underlying defensive reactions (freezing) and actions (avoidance). The behavioral illustrations show the performance of previously acquired reactions (freezing) and actions (avoidance). (**a**) Reactive freezing is underpinned by a progression of information through the amygdala. Information about the auditory conditioned stimulus (CS) arrives in the lateral amygdala (LA) from auditory thalamus and/or cortex. CS information then proceeds to the central amygdala (CeA), either directly through LA projections to the central lateral CeA (CL), or indirectly via the basal amygdala (BA) and/or the intercalated cell masses (ITC). Medial CeA (M) projections to the brainstem coordinate CS-evoked reactions, such as freezing. (**b**) Active avoidance is underpinned by a different amygdalar output pathway. CS information is processed through LA and BA, before progressing to the nucleus accumbens (NAcc), which supports CS-prompted actions, such as shuttling to avoid. This behavior is regulated by the infralimbic prefrontal cortex (PFCIL), which suppresses CeA-mediated freezing.

Neural circuits of avoidance: actions and habits

For reasons articulated above, we emphasize signaled active avoidance studies using a two-way shuttlebox task in which animals learn to avoid a US by crossing a divided chamber when a warning signal (the Pavlovian CS) is present (Figure 1). Much of the historical work on avoidance has used this approach, and the underlying circuits that have been discovered in recent work are illustrated in Figure 3. Where appropriate, we also describe studies that have used avoidance responses such as lever-pressing[27,32] or stepping onto a platform[29,35] to avoid shock in the presence of a CS.

Early neuroscientific studies of avoidance produced confusing results.[68–71,76,77] Damage to a given brain area, such as the amygdala, sometimes disrupted avoidance, sometimes facilitated avoidance, and sometimes had no effect at all. Much of this work involved 'whole amygdala' lesions that spared significant tissue in some cases, while there was significant damage to extra-amygdala regions in others. Contemporary research methods allow for the targeted manipulation of distinct amygdala subnuclei, such as LA, BA and CeA.

Lesion experiments have implicated LA in the acquisition and expression of avoidance responses.[141,142,152] The involvement of this is area is especially significant because it suggests that a CS–US association encoded within LA circuits, is required for both reactions and actions evoked by the CS.[28,152,194] However, reactive freezing and active avoidance depend on different intra-amygdala circuits that emanate from LA.

While connections from LA to CeA provide a key substrate of freezing, lesions of CeA enhance, rather than impair, the acquisition and expression of avoidance.[141,142,195] CeA lesions also rescue performance in animals that fail to express avoidance behavior due to excessive freezing, allowing these 'poor performers' to avoid normally.[141,142] The defensive actions opposed by CeA are underpinned by interactions between LA and BA.[32,141,152,196–198] BA projects robustly to the nucleus accumbens (NAcc).[199–201] NAcc has been implicated in appetitive instrumental behavior,[136,202–207] as have BA neurons that project to NAcc.[205,208–210] Recent findings demonstrate that active avoidance requires NAcc,[29,33,35,211–215] as well as the flow of information from BA to NAcc.[211] Thus, while LA is common to the circuits of reaction and action, distinct outputs of LA give rise to different amygdala output pathways underlying freezing reactions (CeA–PAG) and avoidance actions (BA–NAcc). In the variant of active avoidance conditioning called escape from threat, rats learn to perform actions reinforced solely by CS termination. The amygdala circuits underlying escape from threat mirror those of signaled active avoidance—LA and BA are required, but CeA is not.[152]

Voltammetry studies of dopamine release in NAcc demonstrate interesting similarities between appetitive instrumental behavior and active avoidance. On the appetitive side, it has been shown that dopamine levels begin to ramp up when the subject is presented with a cue that predicts the availability of sucrose, peaking when a lever-press is emitted to obtain that reinforcer.[216] A comparable result has been reported using a lever-press signaled active avoidance paradigm. Presentation of a warning signal elicited an increase in NAcc dopamine, preceding a successful avoidance response. However, if no such dopamine increase was observed, subjects failed to avoid.[27] In a follow-up experiment, presentation of an aversive Pavlovian CS caused a decrease in NAcc dopamine release,[27] suggesting that defensive actions and reactions have a distinct neurochemistry in NAcc. Combined with evidence that BA-NAcc projections have a role in appetitive instrumental action,[205,208–210] these data are consistent with the idea that avoidance is acquired through instrumental learning of an action–outcome relationship.

Lesion and inactivation experiments demonstrate that the infralimbic region of the medial prefrontal cortex (PFCIL) has a key role in the transition from freezing to avoidance.[156] Pre-training lesion or inactivation of PFCIL cause prolonged freezing during training, delaying acquisition of the avoidance response. Once avoidance has been acquired, inactivation of PFCIL impairs the transition from reaction to action, causing a return of freezing, which occludes the avoidance response. Intriguingly, the expression of c-Fos (a marker of neuronal activation) in PFCIL

distinguishes good and poor performers in an unsignaled active avoidance paradigm, in which strong PFCIL recruitment correlates with high avoidance and low freezing.[217] These data suggest that PFCIL functions to suppress defensive reactions and facilitate defensive actions, toggling between behaviors controlled by distinct amygdala output pathways. Thus, PFCIL inhibits behavior driven by the CeA-PAG projection (that is, freezing), facilitating behavior driven by the BA–NAcc projection (that is, avoidance).

But what recruits PFCIL to this task? In the initial phases of training, freezing is high but not total, and many animals will eventually emit the avoidance response randomly. We speculate that these early instances of the response allow subjects to detect the avoidance contingency, engaging PFCIL to initiate the transition from reaction to action. This idea is consistent with previous work implicating PFC in the detection of aversive contingencies.[218] It also explains why poor performers tend to be high freezers[141,142,217] –because of their strong Pavlovian reactions to the CS, these subjects are never able to recruit PFCIL.

The results described so far support the idea that at least two distinct types of learning are at work in the avoidance paradigm. An LA–CeA–PAG pathway mediates the acquisition and expression of CS-evoked freezing. This circuit directly opposes active avoidance, which requires the recruitment of an LA–BA–NAcc pathway later in training. Because defensive reactions and actions are acquired at different points directly conflict with one another, and depend on dissociable circuits, we argue that they are conditioned through two distinct processes. These data provide empirical support for our model, in which the acquisition of defensive reactions is the first factor in avoidance learning, while the acquisition of defensive actions is the second. The first factor is clearly Pavlovian; the second factor may well be instrumental, as suggested by the shared substrates of appetitive instrumental behavior and active avoidance.

In addition to the sequential acquisition of defensive reactions and actions, we argue for a third factor, defensive habit, in avoidance learning. With prolonged training, the avoidance response becomes independent of the amygdala.[142,219] Because both defensive reactions and actions require amygdala circuits, we believe that the transition to amygdala-independent behavior demarcates a habitual phase of avoidance training. Habits are maintained despite a weakened connection with the reinforcing event that initially supported learning.[136–138] The persistence of habit in the absence of reinforcement accounts for the observation that well-trained (habitual) avoidance responses tend to resist extinction, solving what has been considered a conceptual problem in the field.[49,60,62]

Habit learning has been explored extensively using appetitive reinforcers. These studies demonstrate that the initial substrates of instrumental learning give way to a new habit circuitry involving the dorsal striatum.[140,220] Extensive avoidance training may involve a similar transition, moving from outcome-dependent defensive action that involves NAcc to an outcome-independent defensive habit that involves dorsal striatum. Future work should explore the role of the striatal habit circuit in well-trained avoidance behaviors. In addition, activity in the prelimbic region of the prefrontal cortex correlates with avoidance behavior that persists under extinction conditions.[29] We interpret these data to suggest a role for prelimbic prefrontal cortex in defensive habits that continue despite a reduced connection with reinforcing stimuli. This may be relevant to the persistence of avoidance in anxiety disorders, which we will discuss below.

Relatively few studies have examined the brain mechanisms of active avoidance in humans. However, the results from these are broadly consistent with the animal literature. Thus, studies using functional imaging have implicated the amygdala, nucleus accumbens, medial prefrontal cortex and other areas, including habit circuits of the dorsal striatum, in active avoidance in humans.[221–223]

In summary, we argue that avoidance learning proceeds through three distinct phases, each associated with its own neural circuitry. The first phase is Pavlovian, involving defensive reactions underpinned by an LA–CeA–PAG pathway. The second is instrumental and involves defensive actions that require an LA–BA–NAcc pathway. In order to transition from reaction to action, PFCIL is recruited to suppress freezing and facilitate avoidance. The third and final phase involves defensive habits, which are independent of the amygdala and may depend on the dorsal striatum.

THERAPEUTIC IMPLICATIONS

Anxious people often avoid situations in which threats may appear. Avoidance is a very effective way of reducing symptoms associated with fear and anxiety, and avoidant behaviors are negatively reinforced by their success in doing so. But excessive avoidance can also prevent one from learning which situations are actually dangerous. A person with social anxiety who avoids parties loses the opportunity to learn who is friendly and who is not. For good reason, then, avoidance is viewed negatively in the clinical literature.[1–8] The distinction between adaptive and maladaptive avoidance is thus very important.

Discussions of maladaptive avoidance in humans often start with Mower's two-factor fear theory and ways to improve upon it.[52,74,75,224,225] However, we argue that defensive actions like avoidance are reinforced and motivated by nonconscious processes rather than reduction of conscious fear. Evidence from studies of brain-lesioned patients demonstrates that subcortical regions such as the amygdala mediate conditioned defensive responses to threat, but not the conscious experience of fear.[121,122] In place of fear reduction, we reconceive of the reinforcer in avoidance learning as cellular and molecular events in the circuits underpinning defensive action rather than conscious feelings (see above). These changes establish a learned relationship between stimuli and strengthen active responses. This should not be taken to mean that subjective fear has no role in human anxiety and avoidance, but instead that subjective fear reduction is not what causes avoidance to be acquired and sustained. We argue that this view is likely to open more fruitful paths in the effort to understand avoidance.

To pursue the distinction between adaptive and maladaptive avoidance we build on the clinical notion of active and passive coping strategies. With passive coping harm is avoided or postponed by withholding actions to the threat, while active coping avoids harm by performing actions that engage with and control the threat. Active coping strategies help humans adapt and get back to routine life in the aftermath of trauma,[226] and research in patients with anxiety disorders shows the virtues of active engagement as part of the therapeutic process.[4,227] Laboratory analogs of passive coping include freezing and passive avoidance, while active avoidance and escape from threat mirror active coping strategies.

Research on animal behavior has yielded important insights into the brain substrates of active coping. For example, the escape from threat variant of active avoidance conditioning shows how rats learn to perform responses that are negatively reinforced by CS termination. To do this, the passive coping response, freezing, must be inhibited to allow the active coping response to emerge (action cannot be taken while freezing). Through active coping, the animals gain control over the threatening circumstances. This should not mean that active coping is always adaptive and passive coping is always maladaptive. Freezing and passive avoidance are adaptive except when used excessively and begin to interfere with daily life, and active avoidance is adaptive unless avoidance becomes excessive and habitual.

Concepts such as coping and control clearly imply cognitive processes. But the involvement of cognitive processing should not be confused with the involvement of conscious experience.[30] As

we have argued, the learning underlying reactions, actions and habits is implicit; though conscious experiences may occur, they are not the basis of the learning.

Active avoidance paradigms in animals allow us to make two distinctions relevant to clinical problems. First, as noted above, most animals that undergo active avoidance training learn to actively cope with a dangerous situation. A small percentage, though, fail to express active avoidance during and after training. Instead, they exhibit a maladaptive form of coping in which excessive CeA-mediated freezing prevents them from expressing an active, NAcc-mediated avoidance response.[142] By contrast, animals that are able to express an active strategy recruit medial prefrontal cortex, especially PFC_{IL}, to toggle amygdala output pathways—control is shifted from CeA outputs that mediate freezing to the BA outputs that mediate active avoidance. Connections between medial PFC and the amygdala in humans have been implicated in other aspects of emotion regulation in the face of stress.[228,229] A treatment that is able to suppress excessive CeA-mediated reactions might be very useful in facilitating the acquisition of active coping skills in those predisposed toward passive coping. Treatments that enhance medial PFC activity may have a comparable effect. Finally, because NAcc dopamine responses occur on successful avoidance trials, but not when the subject fails to avoid,[27] dopaminergic systems may be another target for therapies designed to facilitate active coping skills.

Second, while overcoming excessive freezing makes active coping possible, active coping itself can be adaptive or pathological. If avoidance, once learned, then becomes excessive, and comes to interfere with daily life, then it loses it adaptive qualities (just as freezing becomes maladaptive when excessive). This typically happens when the avoidance response becomes habitual. When this occurs, another branch point is reached, and there are additional opportunities for both adaptive and maladaptive coping. For example, during flu season, it can be wise to engage in more preventative hand washing than usual in order to avoid infection, particularly if one interacts with a large number of people. In this example, normal life activity is facilitated by an adaptive avoidance behavior. If that same behavior becomes habitual, it serves an adaptive function by not requiring constant intentional control over the behavior. But when it continues even in the absence of any threat because the individual does not take the opportunity to check if circumstances have changed, the habit has become maladaptive. In the case of obsessive-compulsive disorder, hand washing can become excessive and even injurious, persisting regardless of whether there exists any substantial risk of illness. Extinction-resistant forms of habitual avoidance may be particularly relevant to the compulsive behavior observed in many anxiety and addictive disorders.

Studies of active avoidance offer the opportunity to unravel both beneficial and pathological aspects of avoidance. It is the element of controllability, which puts the brakes on reactive defensive behaviors, that makes active avoidance useful. Animals and people who are able to engage in active avoidance may constitute the population of resilient individuals. Understanding the neurological differences underlying adaptive and maladaptive forms of coping may help reveal pharmaceutical or behavioral treatments that facilitate beneficial therapeutic coping strategies.

It is of interest that maladaptive avoidance is not simply a feature of anxiety disorders. It also occurs in people with obsessive-compulsive disorder, depression, suicidal tendencies and autism.[26,230] This is consistent with the idea that pathological avoidance is a domain or dimension[231] spanning several diagnostic categories, rather than a symptom that identifies people with a particular diagnosis.

A final point to consider is whether maladaptive avoidance in humans is based on prior Pavlovian learning. Many have commented on the failure of patients to recount some previous experience that is at the root of their problems.[7,232,233] This is viewed as evidence against a learning account of phobias, for exmaple. But using self-report in this way may underestimate the contribution of prior conditioning. The circuits involved in Pavlovian conditioning, as noted above, operate implicitly and may undergo learning independent of what the conscious mind notices and remembers. Moreover, intensely stressful events can impair memory formation and lead to amnesia for the event. Further, non-associative accounts of phobic acquisition have also been used to dismiss the role of learning.[232] But non-associative accounts are still learning accounts (in other words, non-associative influences on behavior also involve learning). Regardless, the basic neuroscience of how over-responsivity to threats prevents active avoidance, and how the shift from instrumental to habitual behavior maintains maladaptive avoidance, is relevant to these clinical problems.

CONCLUSION

It is safe to say the research on avoidance has finally begun to extract itself from the damaging clutches of criticisms of the past. The new wave of research is showing vibrant signs of life, and beginning to reveal not only interactions between Pavlovian and action learning processes but also the previously unappreciated role of habit learning.

In some sense, the demise of avoidance research several decades ago has resulted in lost time and missed opportunities. But in another sense, it also allowed the field to focus on the neural basis of Pavlovian processes and thereby build up an impressive body of knowledge that is now also aiding the quest to understand active avoidance. The information obtained is allowing active avoidance to be approached with new concepts and new methods, and with new hope for a deeper understanding what avoidance is, how it works in the brain, and how and why it helps some but impairs others in daily life. Better understanding of avoidance circuits will hopefully also lead to new ideas about treatment for maladaptive avoidance, including ways to shift the neural control of behavior in ways typical of resilient individuals.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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