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Pavlovian Fear Conditioning Function, Cause, and Treatment

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Function, Cause, and Treatment

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Fear Conditioning Basics

Pavlovian fear conditioning refers to the learning of associations between nonthreatening environmental stimuli and painful, dangerous or threatening stimulation. With such an experience, these initially nonthreatening stimuli come to elicit a set of new responses that, for the species in question, have been phylogenetically successful in defending against threat (Bolles, 1970; Fanselow, 1984).

In the typical laboratory example of Pavlovian fear conditioning, initially neutral stimuli, such as a brief tone or light, or the conditioning environment itself, is followed closely by an aversive electric shock. These initially neutral stimuli are called conditional stimuli (CS) because they must be experienced in a dependent, or conditional, relationship with the initially aversive "unconditional" stimulus for an aversive response to develop (US; Pavlov, 1927; Rescorla, 1967). When the CS is a brief signal (e.g., a 30-second tone or light), it is referred to as *cued fear conditioning*; when the CS is the static feature of the conditioning environment (e.g., the conditioning chamber), it is referred to as *contextual fear conditioning*. After conditioning, the new learned responses to the CS are referred to as conditional responses (CR), because they are a result of experiencing the dependent relationship between CS and US. Because the responses generated by the US occur independently of experience, they are called unconditional responses (UR). As will be discussed below, CRs and URs are different responses that serve different functions. Rats, mice, and humans are the most frequently used subjects in these studies.

The first laboratory demonstration of fear conditioning is the famous (or infamous) "Little Albert" study conducted by Watson and Rayner (1920). In this study, an infant (Albert) received pairings of a white rat (CS) and loud clanging noise (US). Although discussion of the ethical conduct of this study and questions about the

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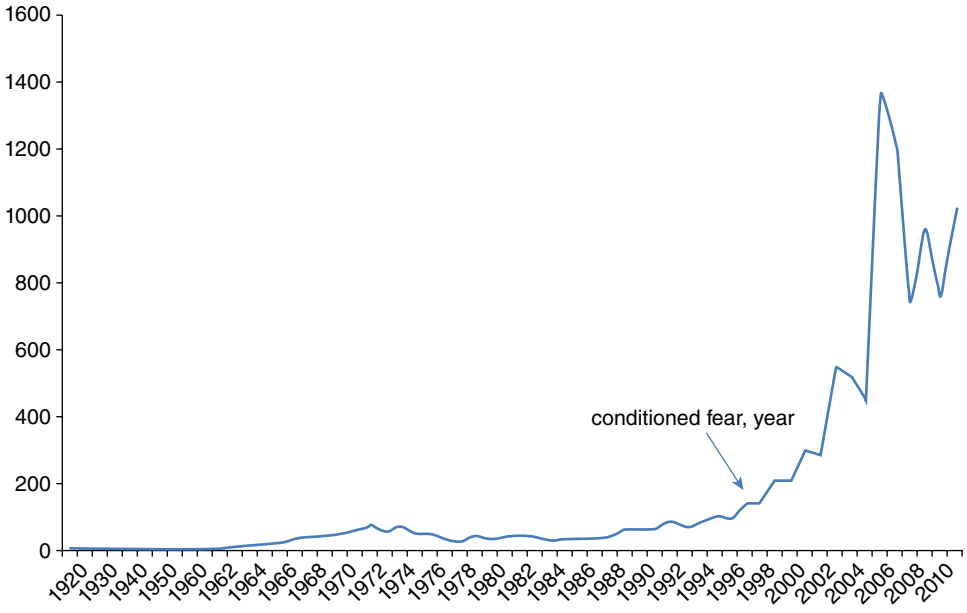

Figure 6.1 Annual number of publications on fear conditioning research since 1900. Data were generated by entering "conditioned," "fear", and a year into PubMed. Any retrieved publications not from the searched year were deleted.

identity of Albert persist to this day (Fridlund, Beck, Goldie, & Irons, 2012; Powell, 2010), one should not lose sight of the fact that the basic effect—learned fear to an initially innocuous stimulus—has been replicated in many species (including humans) under rigorously controlled conditions. Indeed, since 1920 there has been increasing use of the technique with an exponential growth in publications since the millennium, despite the crash of 2008 (see Figure 6.1). The cause of this growth in the rate of fear conditioning research is undoubtedly spurred by its relevance to clinical phenomena and its effectiveness in uncovering the mechanisms of learning. This chapter will deal with these two topics in detail.

Relevance to Anxiety Disorders: More than a Model

Why the prodigious growth in the use of fear conditioning as a research technique? A major reason for this is the relevance of fear to anxiety disorders, such as specific phobia and Post-Traumatic Stress Disorder (PTSD). As a class of psychiatric illness, anxiety disorders cause individuals to suffer from intense, chronic, and impairing anxiety. These disorders can be devastating to the individuals who suffer from them, and their families (McFarlane, 2010; Mendlowicz & Stein, 2000). Anxiety disorders are highly prevalent, with an estimate of 18% in any given year and 28% in the lifetime of an adult American (Kessler et al., 2005). The direct cost of these disorders is a staggering $42–47 billion annually, which jumps to over $100 billion when indirect

costs such as long-term unemployment and co-morbidity with other health problems are taken into account (Greenberg et al., 1999). To gain scientific understanding of anxiety disorders and advancements of treatment, the value of a good animal model is paramount.

Pavlovian fear conditioning allows us to create and treat an anxiety disorder in animals. This might seem like a bold statement, but the core of an anxiety disorder is a powerful fear reaction in situations where such fear is unwarranted. For example, in PTSD, an intensely threatening experience results in aberrant fear responses to reminders of the trauma that last far beyond the event. For the rat, while the typical aversive US, such as a shock, is not particularly painful, it conditions potent fear reactions to innocuous stimuli that last for the lifespan of the animal (Gale et al., 2004). Indeed, one of the earliest laboratory studies of fear noted that the disruption of ongoing behavior produced by the CS far exceeded the disruption produced by the US itself (Estes & Skinner, 1941). Pavlovian fear conditioning in laboratory animals often shows similarities to the pattern of symptom expression found in humans. For example, it has been noted that there is a high correlation between traumatic brain injury and PTSD (Tanielian & Jaycox, 2008). Rats that have received an experimental diffuse traumatic brain injury show enhanced Pavlovian fear conditioning. Laboratory studies can go on to show the causal nature of this linkage between brain injury and how it causes a predisposition to heightened fear (Reger et al., 2012).

Pavlovian fear conditioning is not only relevant to find causes of anxiety disorders; it is also relevant to their treatment. The most effective form of treatment for anxiety disorders is exposure therapy (Norton & Price, 2007; Hofmann & Smits, 2008), which is primarily an application of Pavlovian extinction (Hermans, Craske, Mineka, & Lovibond, 2006; also see Vurbic & Bouton, this volume). Extinction is a new learning that interferes with but does not undo the original learning. This is accomplished by giving repeated presentation of the previously paired CS alone, so that the CS no longer is associated with the US. However, the original learning is not erased, because as time goes by, the original learning, and thus fear, returns (see Vurbic & Bouton, this volume). Thus Pavlovian fear conditioning is more than a model, it allows us to recreate both the cause and treatment of an anxiety disorder in a controlled laboratory setting.

Why are Anxiety Disorders So Prevalent?

The answer to this question requires us to think of fear in its ecological context: What are the costs and benefits of a fear response? Fear is the activation of the functional behavioral system responsible for defense and the principal Pavlovian fear CRs are species-specific defense reactions (Bolles, 1970; Bolles & Fanselow, 1980; Fanselow, 1994). Species-specific defense reactions (SSDRs) are innately organized action patterns that have successfully defended members of the species during their phylogenetic history (Bolles, 1970). Pavlovian fear conditioning activates one of the brain's "survival" circuits (LeDoux, 2012). Therefore, from an evolutionary perspective fear is a good thing; defense in the face of a life threatening danger is one of the greatest biological needs in terms of challenges to reproductive fitness. A single failure to defend against a predator could lead to death, eliminating all chances of future

Table 6.1 Signal detection analysis of the prevalence of anxiety disorders

	Presence of Life Threatening Event?	
	Danger Present	**Danger Absent**
Choose to Defend	Hit Cost: Defensive effort Survival: Possible	False Alarm Cost: Defensive effort Survival: Yes
Choose Not to Defend	Miss Cost: No reproductive future Survival: Unlikely	Correct rejection Cost: None Survival: Yes

reproductive success, while a single missed reproductive or feeding opportunity does not.

Danger must be predicted when possible and Pavlovian fear conditioning allows such prediction. Of course, prediction is rarely perfect in the complex world that mammals inhabit, a danger signal is only probabilistically related to harm. Signal detection theory provides a rubric for understanding prediction in an uncertain world (Peterson, Birdsall, & Fox, 1954; Tanner & Swets, 1954). Obviously, it is advantageous to predict danger when it is present; this is what signal detection theory calls a "hit" (see Table 6.1). Because fear disrupts ongoing behavior (Estes & Skinner, 1941) it has a cost. If no danger is present, it is best not to react fearfully (correct rejection). Both hits and correct rejections are desirable and advantageous. Since prediction is unlikely to be perfect, errors will be made. "Misses" occur when there is danger present but the organism in question does not react to it and the consequences are likely to be catastrophic (e.g., consumption by a predator).

False alarms, responding as if danger is present when there is none, has a cost. Defensive responses require energy and the time spent defending cannot be used for beneficial activities such as mating, feeding, and nesting. However, the evolutionary cost of a false alarm is far less than that of a miss. According to signal detection theory, this difference in cost will cause a shift in criterion leading to a bias in classifying situations with any ambiguity as dangerous, so behavior patterns that lead to a high probability of false alarms will be favored. In a fear situation, frequent false alarms mean frequently reacting to safe situations as if dangerous. The occurrence of such reactions is perhaps the major definitional component of an anxiety disorder, fear, or anxiety in inappropriate situations. Thus natural selection leaves us vulnerable to anxiety disorders (Nesse, 2005). The greater cost of a miss when danger is present leads to the high prevalence of anxiety disorders.

Laboratory Measures of Conditional Fear

Older stimulus-substitution views of Pavlovian conditioning suggested that the CR was a replica of the UR. Pavlov's dogs salivated to both the food and the bell. From this antiquated view, the choice of a measure is easy; simply see how the subject reacts to the US and look for that response when the CS is presented. However, it is well

established that for Pavlovian conditioning there is no general invariant rule relating CR and UR; they may be the similar, they may be of opposing topographies, or they may simply be unrelated to each other (Rescorla, 1988). Rather, a CR can be any response that can be reliably attributed to the previous relationship the organism experienced with CS and US. Estes and Skinner (1941), who developed the first quantitative measure for fear conditioning, recognized both the importance of the CS-US relationship and the lack of correspondence between CR and UR when they stated that, "the disturbing stimulus which is principally responsible does not precede or accompany the state but is 'anticipated' in the future" and "in anxiety, the response which is developed to S1 (*CS*) need not be like the original response to S2 (*US*)" (p. 390).

Insight into choosing a measure of fear can again be obtained by considering the defensive function of fear. If something signals a potential threat to an animal, it needs to (a) stop whatever it is doing, (b) avoid detection or attack, and (c) prepare to react to the threat. These three behaviors underlie the three most common measures of fear. Estes and Skinner (1941), emphasizing the former, measured suppression of ongoing behavior. They did this by first training a rat to lever press for food and then observed the suppression of lever pressing produced by the CS after CS-US pairings. Because moving objects are easier to detect by visual systems, and movement is often the releasing stimulus for a predator's attack of a prey, a dramatic suppression of movement, referred to as freezing, is a reliable and easily quantifiable measure of fear (Fanselow, 1980a; Bolles & Collier, 1976). Freezing is now the most common measure of fear in rats and mice. It has also been shown in humans (Roelofs, Hagenaars, & Stins, 2010). If freezing is not successful and a predator attacks, defensive behavior shifts to explosive reactions to the predator's contact (Fanselow & Lester, 1988). This has been exploited by measuring startle to a loud noise substituted for the shock; fear CSs potentiate startle (Brown, Kalish, & Farber, 1951). This measure has also proven informative in rat and human studies and is currently the most frequently employed measure of fear in humans. Other measures of fear include autonomic changes such as increased blood pressure (e.g., Carrive & Gorissen, 2008), hyperthermia (Godsil, Quinn, & Fanselow, 2000), defecation (Fanselow, 1986) and heart rate (Schreurs, Smith-Bell, & Burhans, 2011), as well as ultrasonic vocalization to warn conspecifics of danger (Lee, Choi, Brown, & Kim, 2001) and analgesia to prevent pain from disrupting defensive behaviors (Bolles & Fanselow, 1980; Fanselow & Baackes, 1982).

In selecting a response measure, several factors need to be taken into consideration. First is the dynamic range of the response. Freezing is very sensitive to low levels of fear, such as those that occur after a single shock. Freezing, as a measure of fear, can discriminate well between different levels except when fear is very high (Fanselow & Bolles, 1979). Defecation can discriminate between no fear and some level of fear but the measure saturates quickly (Fanselow, 1986). Potentiated startle and several measures of avoidance are nonmonotonic with respect to the level of fear and appropriate caution must be used in interpreting the results (Warren & Bolles, 1965; Davis & Astrachan, 1978; Johnson & Church, 1965). Ultrasonic vocalizations are emitted under limited circumstances. Another consideration is that some measures of fear require a probe stimulus that may influence the behavior being measured. For example, analgesia requires administration of a painful stimulus (e.g., radiant

heat, formalin injection, hot plate) that produces pain-related responses. The loud noise used to provoke a startle is sufficiently aversive to support fear conditioning in its own right (Leaton & Cranney, 1990). Some measures (e.g., heart rate, blood pressure, hyperthermia) require invasive manipulations, such as implantations. Conditioned suppression requires the presence of motivation for food or water. Therefore, care must be exerted when response measures are selected.

CS-US Relationships that Promote Cued and Contextual Fear Conditioning

Cued Conditioning

In a typical laboratory fear conditioning experiment, a tone or light will be presented for a period that usually ranges from a few seconds to a few minutes with the shock co-terminating at the end of the interval. Pavlov (1927) referred to this arrangement of stimuli as "delay conditioning" because there is a delay between the start of the CS and the start of the US (see Figure 6.2). The interval between the start of the CS and the start of the US is called the CS-US interval. As is true for most forms of conditioning, this arrangement produces the greatest amount of cued fear conditioning. There is some debate as to why having a short delay between CS and US produces more conditioning than the simultaneous presentation of both CS and US. One explanation is that prediction of the US is the critical factor and delay conditioning allows prediction, while in simultaneous conditioning the CS provides redundant information with the US itself (e.g., Egger & N. E. Miller, 1962). Others have suggested that it is not the amount of learning that causes the difference between delay and simultaneous conditioning but that the difference stems from factors related to the expression of fear. Blaisdell, Denniston, and Miller (1998), have argued that both procedures produce equivalent conditioning but that they are expressed in different

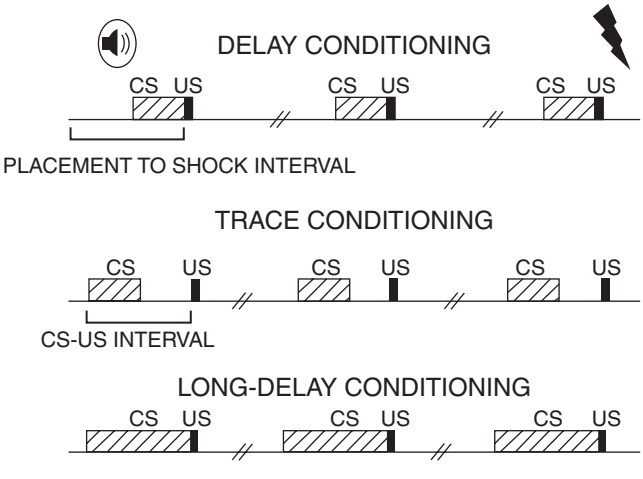

Figure 6.2 Types of Pavlovian conditioning.

responses. However, delay and simultaneous procedures provoke freezing and no one has discovered a response unique to simultaneous conditioning. Furthermore, Blaisdell et al. (1998) used conditioned suppression, and such a nonspecific measure should be disrupted by any fear response. Rescorla (1980) also argued that the superiority of delay conditioning is related to factors that operate at the time of testing. Tests for cued conditioning usually present the CS alone. Rescorla pointed out that means that for simultaneous conditioning the CS presented during test is experienced in a novel way; it is the CS without the US for the first time. This change between training and testing conditions may cause a loss of responding in simultaneously conditioned subjects (i.e., generalization decrement). This is not the case for delay conditioning as the subjects experience the CS alone prior to US delivery during training. Indeed, Rescorla presented evidence that when this change from training to testing is controlled for simultaneous conditioning actually produced better learning than delay. Rescorla's explanation fits well with the fact that although a short delay during training produces maximal expression of fear at test, the longer the delay the weaker the conditioning. The best conditioning will be at a point that strikes a balance between the strong learning that occurs with simultaneity of CS and US and the loss in performance caused by generalization decrement between training and testing conditions.

In delay conditioning there is contiguity between the end of the CS and the start of the US. Conditioning weakens if the CS ends before the US, even if the interval from start of the CS to start of the US is held constant. When the CS ends before the start of the US, there is a brief stimulus-free interval between CS and US. Pavlov (1927) argued that in order for such conditioning to occur some representation of the memory trace of the CS must remain in the brain until the US occurs. Therefore, he labeled this stimulus arrangement as "trace conditioning." While somewhat less robust than delay conditioning, trace fear conditioning can occur at trace intervals at least up to 30 seconds between the CS offset and the US occurring. The deficit in trace relative to delay conditioning is easily overcome if several conditioning trials are used (e.g., 7–10 trials; McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998; Quinn, Oommen, Morrison, & Fanselow, 2002). As will be discussed later, trace conditioning has garnered attention because it recruits additional mechanisms that are not necessary for delay conditioning.

Context Conditioning

In the course of cued conditioning, contextual conditioning will also occur. Despite the fact that both cued and context conditioning occur at the same time, they proceed in very different manners. In general, things that enhance cued conditioning (e.g., shorter CS-US intervals, longer inter-trial intervals, selection of delay over trace procedures) will reduce context conditioning. A useful heuristic for predicting these competition-like effects is the Rescorla-Wagner rule (Rescorla & Wagner, 1972). The model aids in making realistic but counter-intuitive predictions about the effects of adjusting conditioning parameters. For example, by adding more trials one will favor cued over context conditioning. Therefore, if one is interested in maximizing context conditioning but not interested in cued conditioning, one can leave out the cue entirely as this will produce maximal context conditioning (e.g., Fanselow, 1980b).

A critical way that cued and context conditioning differ is with respect to manipulating the delay between the start of CS and start of the US. As described above, performance of cued conditioning degrades as the training CS-US interval lengthens. For context conditioning, the CS-US interval is the time between placement in the chamber and the delivery of shock (placement-to-shock interval, PSI). The PSI function for contextual conditioning is the reverse of the CS-US interval function for cued conditioning (Fanselow, 2010; Wiltgen, Sanders, Anagnostaras, Sage, & Fanselow, 2006). When the PSI is 0 there is no conditioning. This is called the immediate-shock deficit, and it has been demonstrated for freezing, defecation, analgesia, and potentiated startle (Fanselow, 1986; Fanselow, Landeira-Fernandez, DeCola, & Kim, 1994; Kiernan, Westbrook, & Cranney, 1995). Despite the name of the phenomenon, it also occurs with other USs such as a loud noise (Kiernan & Cranney, 1992). A testament to the robustness of the immediate-shock deficit is the finding that when rats received one immediate shock per day for three days they showed no contextual fear. When these same animals were switched to a delayed shock procedure, they acquired freezing at the same rate as shock-naïve rats; there were no savings from the prior three immediate-shock experiences (Landeira-Fernandez, DeCola, Kim, & Fanselow, 2006). The immediate-shock procedure is essentially simultaneous context conditioning, as CS and US onset occurs at the same time, but the absence of conditioning with this procedure contrasts strikingly with the relatively good conditioning that occurs with simultaneous presentation of tone and shock (Fanselow, 2010).

Conditioning increases gradually with lengthening PSI. The animal must configure the elements together into an integrated representation of context; reexposure to the context affords time for the formation of the integrated contextual representation prior to shock delivery, thereby eliminating the deficit. Importantly, pre-exposure to the context must include all features of that context together; separately pre-exposing the individual features (e.g., grid separate from walls) does not confer a benefit (Rudy & O'Reilly, 1999). Such data suggest that exposure allows the features of the context to become associated with each other (Iordanova & Honey, 2012) to form an integrated or conjunctive representation (Fanselow, 1990; Rudy & O'Reilly, 1999). The formation of this representation seems to require active exploration of the context, not simply a passive viewing of the features (McHugh & Tonegawa, 2007).

Biological Mechanisms of Fear Learning

Amygdala As the Hub Of the Circuit

The major components of the neural circuit mediating from environmental stimulation to fear behavior is well established and has been the subject of many reviews (see Figure 6.3; Fanselow & Poulos, 2005; Kim & Jung, 2006; Paré, Quirk, & LeDoux, 2004). Here is only a brief overview. Because fear learning involves the detection of the CS-US relationship, there need to be individual neurons that receive both CS and US information. There are several regions where this occurs but there is a general consensus that the basolateral amygdala complex (BLAC, consisting of lateral and basal nuclei) is the most critical region for this convergence. A long history

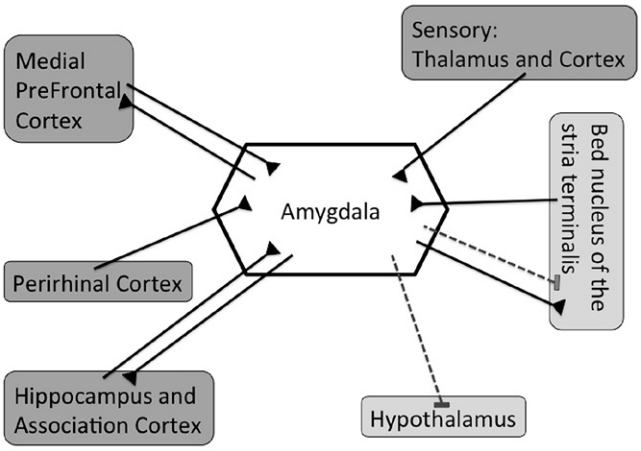

Figure 6.3 A brief overview of fear neural circuitry. Note that solid black lines indicate excitatory projections and dashed gray lines indicate inhibitory projections.

of studies showing that in both human and nonhuman animals, physical damage to the BLAC is devastating to conditional fear (Blanchard & Blanchard, 1972; Bechara et al., 1995; Hitchcock & Davis, 1986). Furthermore, temporarily inhibiting neural activity in the BLAC blocks both learning and expression of conditional fear (Helmstetter, 1992). These studies indicate that BLAC neurons do in fact play a causal role in mediating fear conditioning.

If BLAC neurons are involved in fear learning then it would be expected that BLAC neurons change in response to convergent CS and US information when associative learning occurs. The most promising candidate for the mechanism underlying associative learning is the long-term potentiation (LTP) of the efficacy of glutamatergic synapses (Rodrigues, Schafe, & LeDoux, 2004; Teyler & Discenna, 1984). Induction of LTP requires activation of N-methyl-D-aspartate type glutamate receptors (NMDAR) and application of NMDAR antagonists to the amygdala prior to conditioning prevents fear learning (Fanselow & Kim, 1994; Miserendino, Sananes, Melia, & Davis, 1990).

If NMDAR antagonists are infused into the BLAC prior to an extinction session, they block extinction of a previously conditioned fear response (Falls, Miserendino, & Davis, 1992). Because extinction is a form of associative safety learning (Vurbic & Bouton this volume) and NMDAR are thought to be critical for associative learning, these findings are consistent and suggest that the BLAC is an important site of extinction-related plasticity. However, because extinction does not erase previous fear learning, it is unlikely that acquisition and extinction act on the same glutamatergic synapses as acquisition. One possibility is that, during acquisition, the critical LTP is mediated by glutamatergic synapses on inhibitory neurons in the amygdala (Bauer & LeDoux, 2004; Barash, Bracewell, Fogassi, Gnadt, & Andersen, 1991).

Romanski, Clugnet, Bordi, and LeDoux (1993), provided compelling evidence of CS-US convergence in the BLAC when they made extracellular electrophysiological recordings from the lateral nucleus of the amygdala (LA) and found that both a tone

(CS) and footshock (US) increased spiking in individual neurons in that structure. More recently, Barot et al., (2008) revealed convergence of context and shock information on individual neurons in the BLAC using a very powerful molecular imaging technique for the immediate early gene activity-regulated cytoskeleton protein (Arc) (Guzowski & Worley, 2001). Arc protein is localized to activated glutamatergic NMDARs and is believed to mediate plasticity, as blockade of Arc using an antisense oligonucleotide impaired consolidation of long-term memory (Guzowski et al., 2000). Within a few minutes of relevant activity, projection neurons express Arc. After 20 minutes, Arc RNA is no longer in the nucleus but can be seen in the cytoplasm of the neurons. However, a second bout of neuronal activity will cause a new round of Arc transcription in the nucleus. Therefore, when brains are removed and labeled for Arc RNA, its presence in the nucleus indicates a neuron that was activated 1–5 min earlier and Arc in the cytoplasm indicates neurons activated 20–25 minutes earlier. To take advantage of this time course, Barot et al., (2008) placed rats in a novel context and 25 minutes later gave them a single shock. Compared to several control conditions, these rats showed substantial double-labeling for Arc in both the cytoplasm (corresponding to the onset of context exposure) and the nucleus (corresponding to the time of shock exposure) of basolateral nucleus neurons, indicating CS and US convergence on individual neurons.

Amygdala Afferents

Cued Conditioning. In order to act effectively as a hub structure for fear conditioning, the BLAC must receive the necessary environmental information. Conveniently, the BLAC is a cortex-like structure that receives highly processed information from several cortical and some thalamic regions (see Figure 6.3; Swanson & Petrovich, 1998). CS-evoked activity in several of these areas changes during conditioning (e.g., Edeline & Weinberger, 1992; Gdalyahu et al., 2012). For example, the preferred pitch of auditory responsive neurons shifts toward the frequency of the auditory CS during conditioning (Weinberger, 1993). While these changes probably add information to the fear memory, they do not seem necessary for conditioning to occur (Poremba & Gabriel, 2001; Maren, Yap, & Goosens, 2001).

Auditory information from both the auditory thalamus (medial geniculate nucleus) and auditory cortex arrive at the LA. Both of these routes can support conditioning and stimulation of either auditory pathway can induce LTP in the LA (Clugnet & LeDoux, 1990; Doyère, Schafe, Sigurdsson, & LeDoux, 2003). Visual and auditory information probably gain access to the BLAC via the perirhinal cortex (Kholodar-Smith, Allen, & Brown, 2008; Rosen et al., 1992).

Context Conditioning. The hippocampus also plays an important but relatively select role in fear conditioning. Hippocampal lesions will attenuate context conditioning but leave cued conditioning intact, even though both types of associative learning occurred at the same time (Phillips & LeDoux, 1992). This attenuation is most significant when lesions are made shortly after training (i.e., within a week; Kim & Fanselow, 1992). Lesions made before training or a long time after training have much less effect on contextual fear (see Figure 6.4; Kim & Fanselow, 1992; Maren, Aharonov, & Fanselow, 1997). The finding that increased time between training and lesion decreases the effects of the lesion is consistent with the temporally-graded

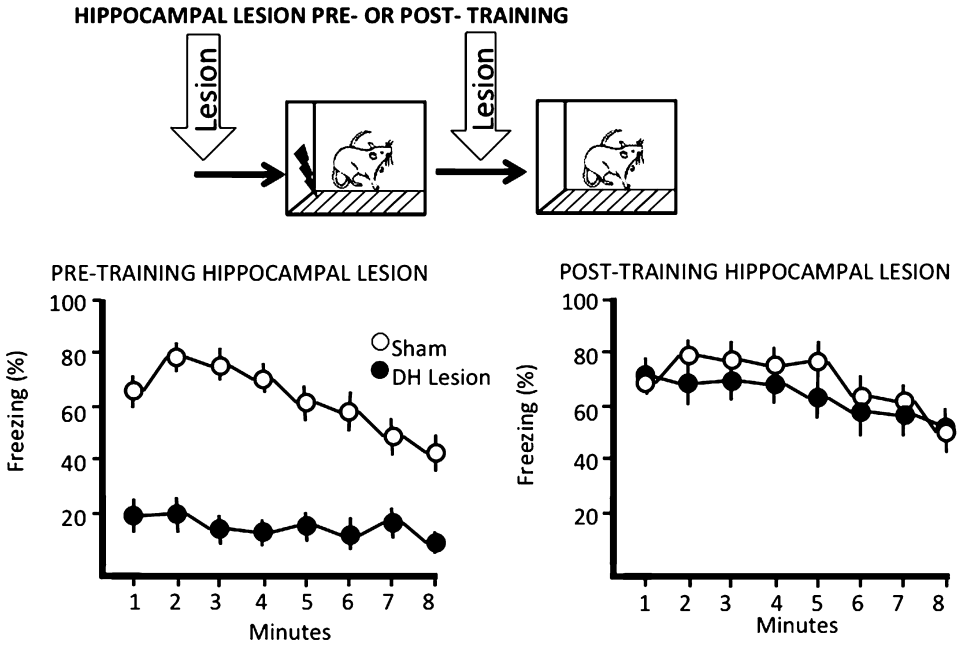

Figure 6.4 Comparing context freezing in rats pre- vs post-training hippocampal lesions. Based on Maren, Aharonov, and Fanselow, (1997) *Behavioural Brain Research, 88*, 261–274.

retrograde amnesia observed in humans for declarative memory following hippocampal loss of function or damage (Squire, 1992). These patients lose memories for events close to the time of brain insult, while older memories are preserved.

The previous section described how context conditioning requires a period of exploration to form an integrated representation of the context. The hippocampus is a good candidate for forming this representation. It is anatomically situated such that it receives highly processed information about the environment (Lavenex & Amaral, 2000). Additionally, rather than responding to simple sensory stimuli, neurons in the hippocampus respond to meaningful stimulus complexes such as being in particular section of a larger environment or a particular person irrespective of vantage point (O'Keefe & Dostrovsky, 1971; Quiroga, Reddy, Kreiman, Koch, & Fried, 2005).

The theory that emerges from these considerations is that long-term synaptic plasticity within the hippocampus underlies the formation of the integrated representation of context (Fanselow, 2000). If this is the case, then manipulations that prevent the acquisition or consolidation of LTP in the hippocampus during context pre-exposure should eliminate the benefit that context pre-exposure has for the immediate-shock deficit. This seems to be true, as both NMDA-antagonists prior to pre-exposure and protein synthesis inhibition immediately after pre-exposure attenuates the enhancement of context conditioning (Barrientos, O'Reilly, & Rudy, 2002; Matus-Amat, Higgins, Sprunger, Wright-Hardesty, & Rudy, 2007).

In this analysis of contextual fear conditioning, it has been suggested that successful context conditioning requires three processes of the animal (Table 6.2). Because

Table 6.2 Simplified environmental processes and brain regions involved in Pavlovian fear conditioning. Abbreviations: conditional stimulus, CS; long-term memory, LTM; medial geniculate nucleus of the thalamus, MGN; lateral geniculate nucleus of the thalamus, LGN; anterior cingulate cortex, ACC; prelimbic cortex, PL

PROCESSES	CUED CONDITIONING	CONTEXT CONDITIONING	TRACE CONDITIONING
	• brief CS signal (such as tone or light) coterminates with a shock	• sufficient time to explore the context to form a contextual representation and store it in LTM	• brief CS signal (such as tone or light)
SUPPORTING BRAIN REGION(S)	• Discrete CS: Thalamic nuclei (MGN, LGN) • CS with co-termination of shock. CS-US Association: Amygdala	• contextual representation: Hippocampus • representation of the context must be in active memory at time of shock: Hippocampus • active representation must be associated with shock. CS-US Association: Amygdala	• Discrete CS: Thalamic nuclei (MGN, LGN) • representation of the context must be in active memory at time of shock: Hippocampus/ prefrontal cortices (ACC, PL) • active representation must be associated with shock. CS-US Association: Amygdala
TEST	• Test cue alone in novel context with no shock	• Test subject in conditioning context with no shock	• Test cue alone in novel context with no shock • Test subject in conditioning context with no shock

hippocampal manipulations made during context pre-exposure influence later performance, the hippocampus is critical to the first process, forming the memory representation of the context. Given the period of exploration during pre-exposure is without shock, such experiments leave open the question of whether or not the hippocampus plays a role in formation of the context-shock association. Tests of this hypothesis took advantage of the fact that hippocampus-dependent memories eventually consolidate to a hippocampus-independent form (Anagnostaras, Gale, & Fanselow, 2001; Young, Boehenek, & Fanselow, 1994). Rats were pre-exposed to one context without shock and then the memory was allowed to age for a month. At that point, when the context representation was presumably consolidated into a hippocampus-independent form, the rats received a context-shock pairing. Lesions of the hippocampus made either before (Young et al., 1994) or after (Anagnostaras et al., 2001)

training did not affect context conditioning in these context pre-exposed rats, while rats that were not pre-exposed to the conditioning chamber were adversely affected by the lesion. Thus context-shock associations can form without the hippocampus, provided the hippocampus previously aided in the formation and consolidation of a representation of the non-emotional features of the context.

As with tone-shock associations, the evidence on context-shock association formation also points to the amygdala (Phillips & LeDoux, 1992). Using the contextual pre-exposure design, one can isolate the time of context-shock association formation by conducting manipulations during the immediate-shock session that follows pre-exposure. Using that approach, Matus-Amat et al. (2007) infused an NMDA antagonist into either the amygdala or hippocampus either before context pre-exposure or immediate shock. The hippocampal manipulation affected test performance if injected before pre-exposure but not immediate shock. BLAC infusions produced the opposite pattern. This experiment provides a clear double dissociation between the amygdala and hippocampus's roles in contextual fear learning. Information about the contextual representations arrives at the amygdala via the ventral angular bundle and stimulation of these afferents supports LTP in the amygdala. Lesions within this pathway attenuate contextual but not auditory conditioning (Maren & Fanselow, 1995). While the hippocampus is important for forming the contextual representation, the amygdala is critical for the context-shock association.

Extinction: Medial prefrontal cortex is strongly interconnected with the BLAC. Rather than carrying simple information about the presence or absence of the CS, these regions typically modulate BLAC. Two adjacent medial prefrontal cortical areas, the infralimbic and prelimbic cortices (IL and PL, respectively), have garnered the most attention as they tend to repress or enhance BLAC activity, respectively (I. Vidal-Gonzalez, B. Vidal-Gonzalez, Rauch, & Quirk, 2006). It is not clear in what situations the prelimbic area acts to enhance fear. Neural activity in the IL occurs during extinction and mimicking this activity reduces responding to a CS (Milad & Quirk, 2002). Thus this region acts to orchestrate BLAC activity most likely by telling the BLAC to not react to CSs that no longer signal threat, particularly after extinction.

Amygdala Efferents

Once the BLAC recognizes that there is danger, it must trigger the full range of fear responses. The nearby medial division of the Central Nucleus of the Amygdala (CEAm) contains projection neurons to many of the downstream structures that generate fear responses including freezing, analgesia, autonomic, and respiration changes and potentiated startle (see Figure 6.5; Fendt & Fanselow, 1999 for a review). Several of the Bed Nuclei of the Stria Terminalis (BST), which communicates with the BLAC and central nucleus, also send parallel projections to these same effector systems (Nagy & Paré, 2008). Current data suggest that CEAm generates a fast but short-lived fear response. In contrast, the BST can produce a more prolonged activation of fear behavior (Waddell, Morris, & Bouton, 2006; Walker, Toufexis, & Davis, 2003).

If fear is recognized by the BLAC, but CEAm generates behavior, the two structures need to communicate. There are multiple routes of communication between BLAC and CEAm that likely serve both fear expression (after acquisition) and fear

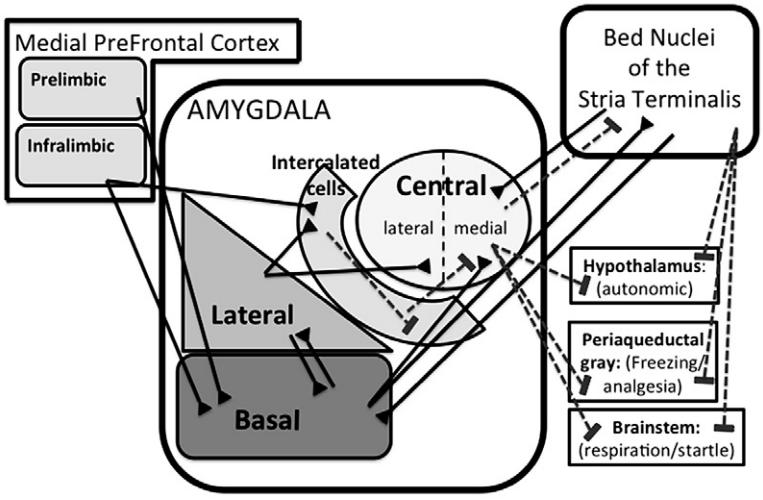

Figure 6.5 A more in-depth view of fear neural circuitry focusing on amygdalar nuclei. Note that solid black lines indicate excitatory projections and dashed gray lines indicate inhibitory projections.

inhibition (after extinction). While the BLAC and CEA are adjacent structures, the fiber tract that separates them contains small clumps of neurons called the paracapsular intercalated cells (PIC; Millhouse, 1986). To understand the function of this circuitry it must be recognized that the cortex-like BLAC consists of excitatory glutamatergic projection neurons and inhibitory interneurons (see Figure 6.5). The CEA is striatal-like and so its projection neurons release the inhibitory transmitter γ-Aminobutyric acid (GABA; Swanson & Petrovich, 1998). The PICs are also GABAergic (Nitecka & Ben-Ari, 1987).

This architecture offers a diverse set of possibilities for the BLAC to influence the CEAm (Carlsen, 1989; Paré et al., 2004). The dorsal part of the BLAC, the LA, does not project directly to the CEAm. However, because this nucleus is critical for auditory fear conditioning, it needs to enforce control of CEAm (Nader, Majidishad, Amorapanth, & LeDoux, 2001). There are three potential pathways for this. The first possibility relies on LA projections to the lateral portion of the Central Nucleus of the Amygdala (CEAl). There are two sets of GABAergic neurons in CEAl that reciprocally inhibit each other and can regulate CEAm output (Haubensak et al., 2010). The LA also projects to the basolateral nucleus and that region projects directly to CEAm (Pitkänen & Amaral, 1991). A third route is via the intercalated cells. The LA projects to a dorsal clump of these neurons, and exciting these neurons would cause an inhibition of the downstream cluster of PIC cells (Paré et al., 2004). This second cluster of PIC cells project to CEAm neurons, so the inhibition of these PIC cells leads to a disinhibition of CEAm neurons, thereby engaging a fear response.

This organization of the BLAC and CEA not only provides a substrate for eliciting fear, it also offers a target for executive regulation of fear by prefrontal cortex. Earlier it was noted that prelimbic (PL) and infralimbic (IL) cortex can upwardly or

downwardly regulate fear responses, respectively (see Figure 6.5). Both of these prefrontal regions project to the basolateral nucleus. The IL, but not PL, also projects to the PIC cells (Berretta, Pantazopoulos, Caldera, Pantazopoulos, & Paré, 2005; Pinard, Mascagni, & McDonald, 2012). Activation of these inhibitory neurons by the IL is one way that the IL may produce the inhibition of fear needed for extinction (Paré et al., 2004).

The Dynamic Origins of Memory Systems (DOMS)

The foregoing section provided a brief overview of how fear circuitry takes in environmental information, processes and stores that information and then generates adaptive behavior. It is important to note that there is no fear "center." Rather, fear is generated by a complex circuit with different aspects of the circuit performing specific tasks (e.g., hippocampus incorporating context and time, the IL inhibiting fear). Often specific locations are described as essential or necessary. The "essential" or "necessary" terminology suggests that if one of these regions is lost the animal should be incapable of performing the function of that brain region. However, the brain is remarkably adaptable and considerable compensation can occur in the face of damage. Rather, these brain regions may be best viewed as normally serving these functions. The compensation is revealed when pre-training and post-training damage are compared.

This pattern first became apparent in studies of hippocampal control over context conditioning. The initial studies used either strong training parameters (15 trials) and made post-training lesions (Kim & Fanselow, 1992) or pre-training lesions with weak training parameters (three or fewer trials; Phillips & LeDoux, 1992). The effectiveness of hippocampal lesions in these early studies led to the interpretation that the hippocampus was essential for contextual fear. However, subsequent studies found the pre-training lesion effect to be variable (Frankland, Cestari, Filipkowski, McDonald, & Silva, 1998). Indeed, Maren et al. (1997) using identical training parameters either before or after a lesion found that pre-training hippocampal lesions had no effect even though post-training lesions abolished contextual fear memory. In general, post-training lesions are uniformly effective regardless of training parameters, while pre-training lesions are very training parameter dependent (Maren et al., 1997). Pre-training hippocampal lesions only affect context fear with minimal training parameters (i.e., when few trials or short context exposures were used). For example, Wiltgen et al (2006) gave 10 conditioning trials to rats and then completely ablated the entire hippocampus. These animals showed no context fear but they were easily retrained to the same level as unlesioned controls. In other words, retrograde amnesia was far greater than anterograde amnesia.

The hippocampus is not the only region where this difference between pre- and post-training lesions was found. Rats with large lesions of the amygdala can acquire fear if substantial overtraining is provided (e.g., 75 shocks; Kim & Davis, 1993; Maren, 1999). Interestingly, rats that receive the same overtraining while intact will completely lose fear if they receive a post-training amygdala lesion or a pretest inactivation of the amygdala (Maren, 1999; Ponnusamy, Poulos, & Fanselow, 2007). Similarly, pre-training lesions limited to the basal nucleus of the amygdala

(Anglada-Figueroa & Quirk, 2005) or the auditory cortex (Boatman & Kim, 2006) do not affect auditory conditioning but post-training lesions of these structures eliminate auditory cued fear.

This pattern of findings has led to a model proposing that there is a dynamic origin to the incorporation of particular neural structures into specific memory systems (Fanselow, 2010). The Dynamic Origin of Memory Systems (DOMS) model starts with the assumption that there are multiple pathways that have potential to mediate between environmental stimulus and adaptive behavior. A common assumption to virtually all theories of memory including DOMS is that these pathways must undergo increases in synaptic efficacy to mediate learned behavior. DOMS assumes that the efficiency of synaptic strengthening varies between these pathways. Unpredicted USs will drive plasticity in these pathways and with each trial the amount of plasticity in a pathway is proportional to the efficiency of the pathway. If the US is fully predicted, that US presentation does not drive synaptic plasticity. If one pathway is highly efficient, it will come to predict the US rapidly leaving little chance for the other pathways to strengthen. We refer to these highly efficient pathways as *primary pathways* because normally they will be the ones that support the majority conditional behavior. If the primary pathway is not available at the time of conditioning (e.g., it has been lesioned or inactivated), the less efficient pathways have the ability to compensate as they are no longer competing with the rapid learning primary pathway. We call these *alternate pathways* as they come into play only when competition with the primary pathway is alleviated. The alternate pathways come to predict the US but because of their reduced synaptic efficiency, they need more training to do so. One should recognize that these ideas are virtually identical to competitive error-correction algorithms that account for stimulus selection in Pavlovian conditioning (Rescorla & Wagner, 1972; Williams, this volume), except that in DOMS, the selection is of neural pathways rather than environmental stimuli. The circuits that perform error-correction in fear conditioning have been characterized elsewhere (Young & Fanselow, 1992; Fanselow, 1998; Bolles & Fanselow, 1980).

DOMS also provides insight into situations where pre-training manipulations are effective. Hippocampally damaged animals that receive minimal training (e.g., one shock) show learning deficits (Rudy, Barrientos, & O'Reilly, 2002) demonstrating the lowered efficiency of the alternate pathways. Genetic or pharmacological manipulations that target long-term synaptic plasticity rather than synaptic transmission also produce profound learning deficits if administered prior to training (Miserendino et al., 1990; Nakazawa et al., 2006). For example, NMDA and cholinergic antagonists, which are both known to prevent LTP, cause profound contextual fear learning deficits if they are infused into the hippocampus prior to conditioning (Gale, Anagnostaras, & Fanselow, 2001; Young et al., 1994). In this case, the primary pathway functions well during learning coming to predict the US and therefore outcompeting the alternate pathways, but the memory formed in the primary circuit cannot be maintained resulting in long-term memory deficits. A nice example of this is provided by Ploski et al. (2008) who used an antisense oligonucleotide to interfere with the immediate early gene Arc. Arc protein accumulates at activated synapses to regulate the expression of AMPA-type glutamate receptors there. Antisense was injected into the LA just prior to conditioning. When tone fear was tested 3 hours after training, fear expression was normal in the antisense-treated rats. Thus, the

primary pathway appeared to be functional during learning. However, when these rats were tested 24 hours later contextual fear was gone. As normally occurs, the primary pathway learned to predict the US giving no opportunity for the alternate pathway to learn. However, the loss of Arc activity in the amygdala meant that the necessary plasticity was not maintained and the result was a loss of long-term memory.

Translational Significance

At the start of this chapter, a case was made for the relevance of Pavlovian fear conditioning to anxiety disorders. The substantial body of research on Pavlovian conditioning has provided detailed insight into the processes and mechanisms that underlie this form of learning. Given these two points, the field should be in a position to apply this knowledge clinically. One arena where this is coming to fruition is combining an understanding of the neural mechanisms with the processes that underlie extinction. As stated earlier, extinction is a new learning that interferes with, but does not undo, the original learning. One clinically problematic aspect of this new learning is that it is context bound. It does not transfer well outside of the original extinction context (see Vurbic & Bouton this volume). Unfortunately, the original fear memory is not so limited and fear will return if the fear CS is presented in any context other than the extinction context (Bouton, 1993). This phenomenon is called renewal and it provides some of the strongest evidence that extinction does not undo the original fear learning. If that were the case, fear should not renew after extinction. This poses a problem for clinical efficacy, as the loss of fear may not generalize out of the therapy context.

One possible way to make extinction more effective is to increase the strength of the extinction learning. Since extinction is mediated by NMDAR in the amygdala, facilitating activity at NMDAR should enhance extinction (Falls et al., 1992). Such a result has been reported for D-Cycloserine (DCS), a positive modulator of NMDAR (Walker, Ressler, Lu, & Davis, 2002). Given that extinction is the source of therapeutic benefit from cognitive-behavioral therapy, the ability to enhance extinction has potential translational impact. Initial reports in human patients have met with some, albeit mixed, success (Guastella, Lovibond, Dadds, Mitchell, & Richardson, 2007; Wilhelm et al., 2008). However, even when DCS treatment facilitates extinction, it does not prevent renewal when the context is changed (Woods & Bouton, 2006; also see Vurbic & Bouton this volume).

To address the context specificity of extinction, a logical candidate is the hippocampus. The hippocampus's role in renewal parallels its role in contextual fear conditioning. Manipulations of the hippocampus can block renewal (Ji & Maren, 2005) and the effects are greater for post-extinction than pre-extinction lesions (Zelikowsky, Pham, & Fanselow, 2012). Obviously, invasive and/or permanent manipulations of the hippocampus cannot be used in a clinical setting. However, systemic administration of very low doses of the cholinergic antagonist scopolamine mimics the effects of hippocampal infusions of the drug on contextual fear conditioning (Anagnostaras, Maren, & Fanselow 1999; Gale et al., 2001). This drug has been used clinically in humans for years to treat sea-sickness, Parkinson's disease and previously, drug addiction. Giving a very low systemic dose of scopolamine during extinction treatment

prevented later fear renewal when rats were tested out of the extinction context (Zelikowsky et al., 2013). It seems that because the rats could not effectively process context during extinction, the extinction memory was encoded in a context independent way. Thus, this treatment holds promise as an adjunct to behavior therapy with the goal of making the loss of fear more general. Ideally, a combined treatment that facilitated extinction learning (such as D-cycloserine in the amygdala), while eliminating its context specificity (like scopolamine in the hippocampus) could be developed.

Conclusions

Fear is a double-edged sword. Because of the evolutionary importance of defense, it must be rapidly turned on when needed and utterly dominate behavior to ensure survival. But there is a downside: fear can be on a hair trigger, especially in those who have experienced previous trauma (Rau, DeCola, & Fanselow, 2005). This, in turn, leads to a high incidence of anxiety disorders. Advances in fear conditioning research have led to an excellent understanding of the behavioral processes and neural mechanisms that mediate fear. Fortunately, this knowledge is being translated to enhance clinical treatment, most notably in terms of adjuncts to extinction-based exposure treatments. Therefore, thanks to fear conditioning research, we should be optimistic that the next years will see a new generation of more efficacious treatments for anxiety disorders.

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