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The place of the hippocampus in fear conditioning

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Abstract

Pavlovian fear conditioning is a phenomenon amenable to laboratory analysis of the neurobiology of fear and the investigation of neural mechanisms of learning and memory. Investigators have made much progress in delineating the neurocircuitry and neurochemistry of fear conditioning. The place of the hippocampus in context fear remains a controversial issue. In this review, we examine the evidence that the hippocampus plays a role in fear conditioning. We then critically examine hypotheses concerning its exact role in learning and memory for cued and context fear conditioning.

Keywords: Fear; Learning; Memory; Amygdala; Hippocampus; Context

1. Introduction

The survival of individuals of all species depends upon the ability to react adequately to threat. Often, this ability hinges upon prediction of aversive events and coordination of defensive reactions in the face of an impending threat. Animals learn to anticipate danger by associating environmental stimuli with aversive events. This associative learning is studied in the laboratory in a procedure referred to as Pavlovian fear conditioning. Pavlovian conditioning has provided a prototype of associative learning for most of the last century and has proven useful for the investigation of the behavioral processes and neurobiological mechanisms of learning and memory. Additionally, the work done on Pavlovian fear conditioning informs the fields of emotional learning and emotional disorders in a direct fashion. Thus, Pavlovian fear conditioning represents an essential area of study for several reasons. It provides a simple, reductive approach for the search for the neurobiological mechanisms of learning and memory and such an understanding is necessary for specific advances in the treatment of emotional disorders.

Pavlovian conditioning provides a simple, tightly controlled behavioral procedure that results in rapid learning. Because of these reasons, the amount of interest in its neural underpinnings has bloomed in recent years.

At this point, we would like to address the role of the hippocampus in Pavlovian fear conditioning. The hippocampus is important for certain forms of memory in humans and has been implicated in particular aspects of learning in rodents. For the past few decades, a number of researchers have sought, in a relatively reductionistic manner, to elucidate the neurobiological underpinnings of various types of learning and memory storage. However, despite the large volume of research, the work done to date on the hippocampus has been far from conclusive. The neural substrates of behavioral phenomena are never simple. Many simple neural structures have very complicated functions. Because fear conditioning provides a very tractable behavioral paradigm, it should be useful in dissecting the role of the hippocampus. Unfortunately, consistent with the larger literature on the hippocampus, research using Pavlovian conditioning has demonstrated that this structure plays a complex but selective role in fear conditioning. This review will attempt to address a number of potential hypotheses concerning the role of the hippocampus in fear conditioning. We will address each in turn, applying as consistently as possible the available literature and noting controversies when they arise.

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2. The basic Pavlovian fear conditioning experiment and its relevance

The Pavlovian conditioning experiment is an investigation of the ability of a subject to learn about the relationships among stimuli. In the typical laboratory experiment, the learning situation is structured such that particular ''neutral'' environmental stimuli predict the occurrence of an aversive stimulus. Such stimuli rapidly acquire the ability to elicit responses that are analogous to natural antipredator defensive behaviors. The experiment often is structured such that the degree of predictiveness varies considerably among the stimuli that are associated with the aversive event. This variety of predictiveness is reflective of the natural defensive situation.

In the laboratory, one often-used experiment is the following: the animal (typically a rodent) is placed in a unique environment (typically an observation chamber with particular lighting, geometry, and odor). After a few minutes of acclimation, a brief stimulus (typically a tone) is presented. At the termination of this stimulus, an aversive stimulus (typically footshock) is presented. The experiment may involve one or repeated pairings of the tone and footshock stimuli. The subject comes to associate the aversive event with both the tone cue and the context in which it is presented. When exposed to these stimuli later, the animal displays natural anticipatory fear responses such as freezing. Freezing is our major dependent measure, being a species-specific defense response in rodent subjects. In Pavlovian terminology, the previously neutral context and tone stimuli are conditional stimuli (CS) and the footshock is an unconditional stimulus (US). That is, the previously neutral stimuli come to elicit defensive behaviors conditional upon their pairing or association with the unconditional stimulus. The US is thus named because its ability to elicit defensive behavior is not conditional upon any prior learning experience. The behaviors that are elicited by the US are called unconditional responses (URs) and the behaviors that come to be elicited by the CS are called conditional responses (CRs).

The structure of the laboratory experiment introduced above closely matches that of the natural environment. The largest threat an animal might face in the environment is predation. In order to survive, an animal must be able to predict its predators. The stimuli in the environment have varied strength in predicting such a threat. Direct contact with a predator elicits unconditional defensive responses. Cues that predict a predator elicit responses conditional upon their predictive validity. Singular cues associated directly with a predator, such as sounds or smells, often are more closely related (temporally speaking) with the actual threat. Just as an animal in the laboratory learns that the tone predicts shock, so the animal in the wild learns that the smell or sound of a predator signals imminent contact. However, the survival of any animal depends on much more than predicting an imminent attack. In order to forage and reproduce successfully, an animal must learn which environments are safe and which are not. Just as the laboratory subject learns which contexts are safe and which are not, the animal in the wild learns which particular places are most predictive of threat.

In light of its similarity to natural learning phenomena, the laboratory experiment, offers a unique opportunity for the investigation of fear and anxiety disorders. Human fear and anxiety disorders can be viewed quite simply as disorders in the prediction of threat. Human anxiety disorders run the gamut from abnormal fear of particular stimuli, as occurs with phobias, to abnormal fear of external environments, as occurs with agoraphobia. In the laboratory, we can achieve tight control over which stimuli are predictive of threat. Thus, we can control the stimuli that elicit fear responses. Our hope in the laboratory is that we can delineate the neurobiology of fear. In outlining the natural circuitry and neurochemistry of fear learning, we likely will discover the very circuitry and neurochemistry that is dysfunctional in fear and anxiety disorders.

In this light, we would like to discuss the role of a particular structure, the hippocampus, in fear learning. Recent advances in the laboratory have sharpened our knowledge of the role of the hippocampus in fear. However, certain results also have forced us to rethink the role of the hippocampus. Until very recently, our knowledge of the role of the hippocampus came from lesion studies. Lesion studies often tell us that a structure is important in particular behaviors. Less often, however, do lesion studies inform us of the particular process subsumed by the structure. Recent pharmacological advances allow us another level of control in the laboratory and allow us to examine more closely the part played by particular brain structures in fear and anxiety.

3. The neurocircuitry of fear conditioning

It is important to recognize that memories do not reside in a single anatomical locus but rather arise from interactions among a number of structures that compose a neural circuit. When neuroscientists speak of circuitry, they often speak of inputs, outputs, and memory systems that allow for adaptation of responses to the environment. One pivotal component of the fear circuit is the amygdala (for reviews, see Maren, 2001a; Fanselow and LeDoux, 1999). Amygdala lesions are devastating to both the acquisition and expression of fear conditioning (Maren et al., 1996a; LeDoux et al., 1990). Blockade of neural activity and plasticity in the amygdala prevents fear conditioning to all CSs (Helmstetter and Bellgowan, 1994; Maren et al., 1996b; Wilensky et al., 1999). Fear conditioning causes changes in amygdala neurons (Quirk et al., 1995; Maren, 2001b). Available evidence suggests that the amygdala is a critical site of plasticity for the formation and storage of fear memories generally. In this light, other structures can be viewed as stimulus processing inputs to the amygdala or outputs necessary for the produc-

tion of defensive behaviors. Considerable data indicate that the hippocampus normally is involved in the neural circuitry of fear conditioning. However, its place might lie anywhere along the pathway between an experience with environmental events and the production of adaptive behavior in response to those events. Put simply, the hippocampus may be a sensory relay, a motor relay, a site of information storage, or any combination thereof. Obviously, the hippocampus may share any or all of these duties with other structures. We will entertain here a series of hypotheses about the role of the hippocampus in the circuitry of conditioned fear, from input to output. Some of these hypotheses are more tenable and some are less so. In each case, advances in pharmacological techniques have led to reformulations of previous hypotheses.

4. Hippocampus as an input structure in fear conditioning

One possibility is that the hippocampus is a simple relay for visuospatial, auditory, olfactory, or other sensory input important for fear conditioning. Clearly, the rodent hippocampus receives multimodal sensory information. The long study of place cells within the hippocampus proves that, at the very least, the hippocampus processes visuospatial information (Rotenberg and Muller, 1997). More recent data from the hippocampal electrophysiology literature indicate that other stimuli affect the performance of cells within the hippocampus. These stimuli include olfactory stimuli (Eichenbaum et al., 1987; Wood et al., 1999) and auditory stimuli (Edeline et al., 1988; Luntz-Leybman et al., 1992; Adams and Stevens, 1998). The question before us now is whether or not the hippocampus simply serves to relay this sensory information to another part of the fear circuit that serves a mnemonic and/or output function. Pre- and post-training lesions of the hippocampus can disrupt context fear conditioning (Kim et al., 1992; Young et al., 1994; Maren et al., 1997). These effects are consistent with a purely sensory role for the hippocampus in fear conditioning. Pre-training lesions obviously would disrupt transmission of vital sensory information during acquisition. Post-training lesions would disrupt sensory processing during the test phase and thus disallow proper recall of the conditioned stimuli. However, one observation argues against a simple sensory role for the hippocampus: post-training lesions are not effective if delayed for a considerable time after training (Kim and Fanselow, 1992; Maren et al., 1997). More recently, Sacchetti et al. (1999) reported that post-training infusions of tetrodotoxin (a Na^+ channel blocker) into the dorsal hippocampus blocked consolidation/storage of memory for fear conditioning. These investigators showed that dorsal hippocampal infusions of tetrodotoxin reduced context fear conditioning when given 90 min or less after the conditioning event. Therefore, given sufficient time between training and lesion, performance of context fear becomes independent of the hippocampus. These data are not consistent in any way with the argument that the hippocampus is a sensory relay. Rather, they clearly indicate that the hippocampus is involved in fear conditioning processes outside the presence of the stimuli used to condition fear. Furthermore, the tetrodotoxin-sensitive processes within the hippocampal formation appear to be important only within a couple of hours of the learning event, while the lesion data indicate that hippocampal processes are important for a much longer period of time.

5. Hippocampus as an output structure in fear conditioning

Could the hippocampus simply be a relay for creating defensive responses? Lesions and other manipulations of the hippocampus result in alterations of motor behavior both in particular tasks (such as fear conditioning) and in open arenas. The crucial question at hand is whether the hippocampus can be characterized as a structure that is involved primarily in the production of defensive behaviors.

Pre-training electrolytic hippocampal lesions, which result in increased locomotor activity, also result in impairment in context fear conditioning (but no effect on tone conditioning) (Young et al., 1994). This increased locomotor activity could indicate that the hippocampus is important for organizing the fear response itself. However, data from neurochemical manipulations provide evidence that the role of the hippocampus is not so simple. An interesting recent paper by Bailey et al. (2002) reports that manipulation of gamma-aminobutyric acid (GABA) transmission within the hippocampus can cause a fear response prior to the administration of any footshock. The novel GABA receptor inverse agonist, RY024, caused both an increase in fear-related behavior before footshock administration and a reduction in conditioned fear when animals were tested later off drug. If the only action of this compound was to increase fear, then there should have been a clear enhancement of fear conditioned to the training context. However, the impairment in context conditioning indicates one of two things: either the fear-related behavior seen before shock administration was not fear per se but some simple motor effect or the drug affected some mnemonic process that reduced context conditioning despite the increase in fear caused during acquisition. Regardless, even if the baseline fear effects were due entirely to motor disruption, the drug reduced context fear conditioning. Thus, the hippocampal processes affected by the drug were not simply motor output processes.

Recent data from a series of studies involving infusions into the ventral hippocampus indicate that manipulations that reduce uniformly context fear conditioning can have more diverse effects on motor behavior. Infusions of both tetrodotoxin and muscimol reduce locomotion in the open field and impair context conditioning (although tetrodotoxin also affects tone conditioning) (Bast et al., 2001). (5R,10S)-

(+)-5-Methyl-10,11-dihydro-5*H*-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (MK-801) likewise reduces context fear conditioning but results in an increase in locomotor activity (Zhang et al., 2001). Hippocampal lesions and hippocampal administration of pharmacological agents have varied behavioral effects. Overall, no clear relationship can be discerned between the behavioral effects of these interventions and the mnemonic effects of these interventions. Thus, we are led to the conclusion that the role of the hippocampus in fear conditioning is not as a motor output structure.

6. Hippocampus as a memory structure in fear conditioning

Could the hippocampus store critical information that is important for fear conditioning?

6.1. Evidence from electrolytic and excitotoxic lesions

Lesions of the hippocampus made after training are devastating to the performance of context fear but leave undisturbed the performance of tone fear (Kim and Fanselow, 1992). These early data are consistent with the hypothesis that the hippocampus stores some information that is vital selectively to the expression of context fear. Note that this evidence is not consistent with the hypothesis that the hippocampus is necessary for the motor components of the response, as tone fear expression is intact. They also are not consistent with the hippocampus storing associations between neutral stimuli and footshock because at least some CS–US associations (i.e. tone-footshock associations) survive its ablation. However, this does not rule out the possibility that the hippocampus is critical for memories for aspects of fear conditioning other than those involving footshock. The context CS really is a combination or configure of the many stimuli that comprise the learning environment (visuospatial, olfactory, auditory, etc). In order for context conditioning to proceed, the various stimuli in the environment must be associated with one another as the context. Therefore, we have proposed that one function of the hippocampus is to assemble a contextual representation, which itself can become associated with the footshock US (see Fanselow, 2000 for review). Thus, plasticity and memory mechanisms within the hippocampus are fundamental mechanisms in the neural circuitry of fear conditioning. Pre-training electrolytic lesions of the hippocampus attenuate acquisition of context fear (Kim et al., 1993; Young et al., 1994) and plasticity within the hippocampus is necessary for fear conditioning to proceed (Young et al., 1994). This plasticity likely is responsible for the assembly and/or storage of the context representation. The early lesion data (Kim and Fanselow, 1992) indicated that the hippocampus is necessary for context memory for a limited time after conditioning. Thus, the hippocampus stores information that is necessary for a coherent representation of context (at least) but this information is needed only for a limited time after conditioning. At some point after conditioning, this context representation is stored outside of the hippocampus.

More recent data from studies using neurotoxic lesion techniques largely have confirmed, but occasionally have challenged, our previous hypotheses of hippocampal function in fear conditioning. Maren et al. (1997) reported an extensive investigation of the effects of *N*-methyl-D-aspartic acid (NMDA) lesions of the dorsal hippocampus. They made lesions of the dorsal hippocampus before training in some animals and after training in others. As with the Kim and Fanselow experiments, post-training lesions caused deficits in fear conditioning and indicated that the hippocampus has an important but time-limited mnemonic role. Unlike the Young et al. experiments, pre-training lesions failed to affect context fear. However, pre-training and post-training lesions of the dorsal hippocampus produced a modest tone-conditioning deficit. Heretofore, tone-conditioning deficits were seen with neither pre- nor post-training electrolytic lesions of the dorsal hippocampus. Obviously, these findings complicate matters considerably. The hippocampus does not always seem to play a role in context conditioning and sometimes appears to be involved in tone fear.

These complexities are beginning to be understood. The finding of a tone deficit seems to be related to the nature of the tone test procedure. Typically, tone testing in these experiments has followed the procedure used by Kim and Fanselow (1992), where the tone used for testing is much longer (8 min) than the tone used for training (30 s). Kim and Fanselow (1992) chose this procedure to make the tone test analogous to the long period used to test context fear. In the Maren et al. study, hippocampal lesioned rats showed deficits toward the end of the test, at a time period considerably beyond when the tone would have terminated during acquisition. However, testing may be done with a CS of the same duration as that used during training (e.g., Fanselow and Bolles, 1979). During short tests, tone deficits are not observed in animals with pre-training hippocampal lesions (e.g., Phillips and LeDoux, 1992). A recent study provides insight into the difference between long and short tone tests. Quinn et al. (2002) examined the effects of post-training excitotoxic lesions on a number of conditioning procedures that included standard tone conditioning. They used a short tone presentation during testing rather than the longer tone that typically is used in our laboratory. Hippocampal lesions reduced context freezing, confirming the role of the hippocampus in context fear. Hippocampal lesions had no effect on freezing during tone presentation, indicating no role for the hippocampus in tone fear. However, hippocampal lesions reduced freezing significantly during the first minute after the tone presentation. Quinn et al. argued that this freezing was not mediated by a tone-shock association because the same pattern happened in a separate group of rats that had received backward pairings of the tone and shock (which

leave no basis for the tone to be a predictor of shock). They suggested that the tone may act to remind the rat of the context in which conditioning occurred. Such context conditioning would be dependent upon the hippocampus. When long tone tests are used, the measurement period includes the epoch that would have constituted the inter-trial interval during acquisition. Thus, the tone deficit observed by Maren and others during long tone tests may be a deficit in this sort of contextual memory and not a deficit in associative tone responding per se. Much work lies ahead in delineating when and how the hippocampus is involved in memories for discrete stimuli, but it seems likely that the tone effects are not deficits in a tone-shock association.

In addition to controversies surrounding the type of stimuli processed by the hippocampus, much confusion persists about whether or not the hippocampus has an obligatory role in fear conditioning. As we stated above, while hippocampal lesions made a day after training are devastating to context fear, pre-training hippocampal lesions have a less robust effect. Studies of retrograde amnesia provide insight into this discrepancy. Post-training lesions do not produce a deficit in context conditioning if they are delayed considerably after training. This finding has always been taken to indicate that contextual memories are stored in regions outside the hippocampus. Thus, there are at least two anatomical regions that can store contextual memories. O'Reilly and Rudy (2001) have proposed a quantitative model that suggests that these two regions are the hippocampus and the neocortex and that they have different operating characteristics. Their model suggests that the hippocampus is ideal for the rapid, incidental learning that is needed for context conditioning. Similarly, we (Fanselow, 2000) proposed that the hippocampus normally forms the contextual representation but the neocortex can serve this function in its absence. Additionally, we have suggested that the hippocampus inhibits the cortex from forming a redundant representation. If the hippocampus is intact during training but lesioned a day later, the animal is left without the memory that was originally learned and stored by the hippocampus. If the hippocampus is lesioned prior to training, the cortex is released from hippocampal inhibition and is able to acquire and store the contextual memory. As stated above, a modest deficit may be observed with pre-training hippocampal lesions. This modest deficit may indicate that the operating characteristics of the neocortex are not ideal for contextual learning (O'Reilly and Rudy, 2001).

6.2. Evidence from infusions

Electrolytic lesions of a neural structure cause damage within the structure and also destroy fibers of passage. This fiber damage makes conjecture about the function of the cells within the target structure difficult. Excitotoxic lesions of the same structure can prevent the loss of fibers of passage and can reveal more directly the role of a particular brain region. However, as we have argued recently (Anagnostaras et al., 2002), excitotoxic lesions can cause difficulty in interpretation as well. Excitotoxic lesions can cause over-excitation of downstream structures such that the lesion may result in damage to the area of interest but also dysfunction in the next stage of the particular circuit. Thus, one can determine through excitotoxic lesions that a particular target structure is part of a circuit that is important for fear conditioning. However, the exact place and role of the target within the circuit is left open to interpretation. Temporary inactivation and neurotransmitter blockade, via targeted pharmacological intervention, provide significant advantages in discovering the precise functions of nuclei within the circuit underlying fear conditioning. Each technique has its own advantages and disadvantages, and therefore the role a particular structure plays within a functional circuit is most profitably analyzed with a combination of techniques.

Our laboratory has undertaken a series of infusion studies aimed at delineating the neurotransmitter and plasticity mechanisms in the dorsal hippocampus that may underlie fear conditioning. Gale et al. (2001) infused scopolamine into the hippocampus before placing rats in the conditioning chamber. The drug had no effect on the unconditional response to footshock but did reduce both post-shock freezing (i.e. short-term memory) and later context freezing (i.e. long-term memory). Scopolamine infusion had little effect on tone fear. Thus, cholinergic mechanisms in hippocampus are involved in acquisition of context fear. Another recent paper indicates that cholinergic mechanisms also are involved in consolidation of context fear. Wallenstein and Vago (2001) administered scopolamine to the hippocampus either before or after animals received five tone-shock pairings. Animals in their anterograde group received drug 15 min before conditioning. As in the Gale study, these animals showed a large deficit in context fear but no deficit in tone fear. Animals in their retrograde group received drug thrice: at 1 min, 24, and 48 h after conditioning. Animals in this group also showed profound deficits in context fear but not tone fear. Thus, cholinergic processes in the hippocampus are involved in memory for context fear. In addition to cholinergic processes, serotonergic processes have been implicated in acquisition of context fear. In mice, dorsal hippocampal administration of a 5-HT_{1A} receptor agonist before conditioning reduced context fear significantly (Stiedl et al., 2000). An important series of studies have begun to investigate the role of ventral hippocampal neurotransmission in fear conditioning. Infusion of the GABA receptor antagonist muscimol into the ventral hippocampus of rats causes a selective impairment in the acquisition of context fear (Bast et al., 2001). This result indicates that cells of the ventral hippocampus are involved in the mnemonic processes underlying context fear conditioning. Importantly, the same paper reported that tetrodotoxin administration into ventral hippocampus impaired both context and tone fear. As tetrodotoxin acts on Na^+ channels

at the axon, this impairment likely was due to inhibition of signals in fibers of passage.

The method by which the hippocampus acquires, consolidates, and perhaps stores information likely involves the NMDA receptor. Dorsal hippocampal administration of DL-2-amino-5-phosphonopentanoic acid (APV), an NMDA receptor antagonist, impairs acquisition of context fear but leaves tone fear intact (Young et al., 1994; Stiedl et al., 2000). Likewise, ventral hippocampal administration of MK-801, another NMDA receptor antagonist, impairs context fear conditioning selectively (Zhang et al., 2001). We have argued that an LTP-like mechanism, involving the NMDA receptor, underlies both the acquisition and consolidation of contextual information in the hippocampus and the acquisition and consolidation of CS–US association in the amygdala. Manipulations of plasticity in the hippocampus therefore selectively affect contextual learning while such manipulations in the amygdala affect both context and tone conditioning (Lee and Kim, 1998; Fanselow and Kim, 1994). Clearly, the hippocampus is a major player in the mnemonic processes that underlie acquisition, consolidation, and (at least for some time) retrieval of context fear. Additionally, there may be some conditions under which hippocampal processes underlie memory for simple stimuli such as a tone. However, we are much more confident that the hippocampus plays a major role in contextual learning.

7. Summary

In conclusion, we are convinced that the hippocampus plays a vital role in Pavlovian fear conditioning. Combining more sophisticated behavioral analysis with lesion and pharmacological techniques have cleared up some of the confusion that resulted from the initial studies in this area. These studies indicate that the hippocampus normally mediates the acquisition and consolidation of a memory for the conditioning context. Other structures, presumably the neocortex, store this memory once hippocampal consolidation is complete. When hippocampal damage occurs before learning, these very same cortical structures may compensate for its loss. We are learning more about which neurotransmitter systems and which cellular plasticity mechanisms are employed by the hippocampus in fear conditioning. Undoubtedly, these mechanisms will prove important in other learning systems. More importantly, however, these systems well may prove to be the very systems whose dysfunction underlies fear and anxiety disorders. The search for the circuitry and pharmacology of fear is a tandem, cooperative effort: studies aimed at the pharmacology of fear will reveal much about the circuitry of fear. Studies of the circuitry of fear will lend insight into the most appropriate pharmacological strategies for dealing with dysfunction in the fear system. With recent advances in behavioral, neurosurgical and neuropharmacological techniques, we believe that the coming years will be an exciting and exceptionally fruitful period for work on the neurobiology of fear.

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