Recalling Safety: *Cooperative Functions of the Ventromedial Prefrontal Cortex and the Hippocampus in Extinction*

By Kevin A. Corcoran, PhD, and Gregory J. Quirk, PhD

ABSTRACT

Anxiety disorders are commonly treated with exposure-based therapies that rely on extinction of conditioned fear. Persistent fear and anxiety following exposure therapy could reflect a deficit in the recall of extinction learning. Animal models of fear learning have elucidated a neural circuit for extinction learning and recall that includes the amygdala, ventromedial prefrontal cortex (vmPFC), and hippocampus. Whereas the amygdala is important for extinction learning, the vmPFC is a site of neural plasticity that allows for the inhibition of fear during extinction recall. We suggest that the vmPFC receives convergent information from other brain regions, such as contextual information from the hippocampus, to determine the circumstances under which extinction or fear will be recalled. Imaging studies of human fear conditioning and extinction lend credence to this extinction network. Understanding the neural circuitry underlying extinction recall will lead to more effective therapies for disorders of fear and anxiety.

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Needs Assessment

Exposure-based (extinction) therapies are commonly used in the treatment of fear disorders. Individual neural structures important for various stages of fear learning, extinction, and extinction recall have been identified, but the functional interactions between these structures in mediating these processes is less known. In this review, we probe the role of hippocampal-prefrontal interactions in the recall of fear extinction.

Learning Objectives

At the end of this activity, the participant should be able to:

- Identify neural structures essential for fear learning and expression.
- Identify a network of brain regions important for the acquisition and recall of extinction memory.
- Recognize causes for relapse of fear after extinction.

Target Audience: Neurologists and psychiatrists

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INTRODUCTION

Animal models of learned fear provide insight into the behavioral and neurobiological substrates of fear and anxiety disorders in humans. In Pavlovian fear conditioning, for example, a conditioned stimulus (CS), such as a tone, is paired with an aversive unconditioned stimulus (US), such as a footshock. As a result, later presentations of the CS elicit a constellation of behavioral and physiological fear responses.[1] The association between CS and US is rapidly learned,[2,3] and fear to the CS is expressed independently of when[4] or where[5] it is presented.

From a clinical standpoint, it may be more important to understand how fear is unlearned. How does a traumatized individual learn to extinguish fear responses? In animal models of fear, "extinction" is described as a reduction in the amplitude and probability of fear responses as a result of nonreinforced presentations of a CS.[6,7] Unlike the recall of fear associations, the recall of extinction is labile; several manipulations cause a return of fear after extinction.[8] Extinction recall is disrupted when the CS is presented outside the context in which extinction took place,[9,10] a process termed "renewal." The passage of time can also impair extinction recall, causing the "spontaneous recovery" of fear responses.[11,12] These phenomena suggest that reduced fear responding during extinction is not due to a loss of the CS-US association, but to new learning (eg, a CS-"no US" association) that inhibits the expression of the conditioning memory.[6,11,13,14] Following extinction conditioning, memory is present but is not recalled. In a similar way, renewal and spontaneous recovery represent failures to recall extinction rather than a loss of extinction memory.[6,11] Thus, following fear conditioning and extinction, both memories are present and their expression is gated by neural systems that mediate context-appropriate recall.

Failure to recall extinction has been cited as a reason for persistent fear in disorders such as post-traumatic stress.[15,16] In this review, we will outline a neural circuit that subserves extinction recall in rats, which includes the amygdala, ventromedial prefrontal cortex (vmPFC), and hippocampus. Our goal is to use data gathered from animal models of fear learning and extinction to help understand why people suffering from fear and anxiety disorders fail to recall extinction.

THE AMYGDALA IS A SITE OF PLASTICITY FOR FEAR AND EXTINCTION

The amygdala is a critical site of plasticity for fear learning.[17-21] Given its pivotal role in fear learning and expression, it is not surprising that the amygdala is also a site of plasticity in extinction learning. Acquisition of extinction requires *N*-methyl-D-aspartate (NMDA) receptors in the amygdala[22] that activate intracellular signaling cascades,[23-25] leading to the synthesis of new proteins.[24,25] One such protein is the γ-aminobutyric acid (GABA) clustering protein gephyrin. Fear conditioning decreases levels of gephyrin in the basolateral amygdala, and extinction learning is correlated with a return to baseline levels of gephyrin and an increase in the surface expression of $GABA_A$ receptors in the amygdala.[11] Thus, extinction memories are represented as increases in inhibitory neurotransmission within the amygdala.[28] Extinction recall, therefore, reflects the degree to which this inhibitory memory, as opposed to the excitatory conditioning memory, is activated.

THE VENTROMEDIAL PREFRONTAL CORTEX IS A SITE OF PLASTICITY FOR RECALL OF EXTINCTION

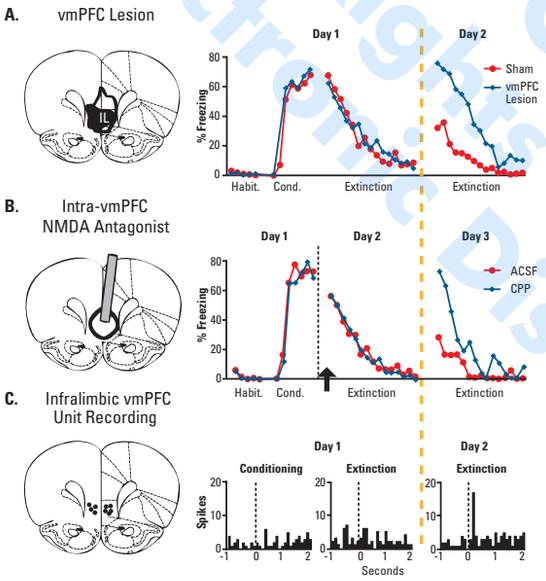
Because the amygdala controls fear expression, regulating amygdala activity represents one way to regulate fear. One structure that is uniquely situated to regulate activity in the amygdala is the vmPFC. The infralimbic subregion of the vmPFC projects to GABAergic cell groups within the amygdala[29-31] that have been shown to inhibit amygdala output.[32] Indeed, infralimbic stimulation activates inhibitory cells within the amygdala and inhibits amygdala output,[33,34] supporting a role for infralimbic subregion in fear inhibition.[35]

Accumulating evidence from behavioral studies indicates that vmPFC is essential for the recall of extinction memory (Figure 1). Rats with vmPFC lesions are able to learn extinction within a single session, but are unable to recall extinction the following day.[36,37] Moreover, intra-vmPFC administration of NMDA receptor antagonists[38] or protein synthesis inhibitors[39] does not impair extinction learning but leads to a failure to recall extinction the following day. More recent findings also implicate vmPFC in recall of extinction of other types of conditioned fears. Blockade of cannabinoid-type 1 receptors in vmPFC similarly disrupted extinction recall in a fear-potentiated

startle experiment,[40] whereas potentiation of α–amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors facilitated learning and recall of context fear extinction.[41] These results indicate that synaptic plasticity in this region is essential for the later recall of extinction.[42] Neurons in infralimbic subregion of the vmPFC do not signal the CS during conditioning or extinction learning, but are active the day after extinction training when rats are recalling extinction,[43] suggesting that these neurons signal extinction recall.

Though manipulations of vmPFC impair recall of extinction, they do not eliminate extinction memory entirely. When rats are re-extinguished during testing via additional CS presentations, extinction proceeds at a faster rate than during the original extinction training (Figure 2).[37,38] This faster rate of re-extinction is evidence of "savings" of the original extinction memory, which is presumably stored in the amygdala. Thus, vmPFC is not necessary for the acquisition or storage of the CS-"no US" memory learned during extinction. Rather, extinction-related plasticity in vmPFC is necessary for recalling extinction at a later time.

FIGURE 1.
Plasticity in vmPFC is essential for extinction recall but not extinction learning



(A) Permanent lesions of vmPFC or (B) infusion of the NMDA receptor antagonist CPP into vmPFC do not interfere with extinction learning within a session. The following day, however, these rats exhibit increased fear responses, indicating deficient extinction recall. (C) Neurons in the infralimbic subregion of vmPFC increase their firing rates during the recall of extinction, but not during fear conditioning or extinction training.

(A) Adapted from Quirk GJ, Russo GK, Barron JL, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *J Neurosci.* 2000;20:6225-6231. Copyright (2000); (B) Adapted from Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ. Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. *Neuron.* In press. Copyright (2007); (C) Adapted from Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature.* 2002;420:70-74. Copyright (2002).

vmPFC=ventromedial prefrontal cortex; NMDA=*N*-methyl-D-aspartate; ACSF=artificial cerebrospinal fluid; CPP=d(-)-3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid; Habit=habituation; Cond=conditioning.

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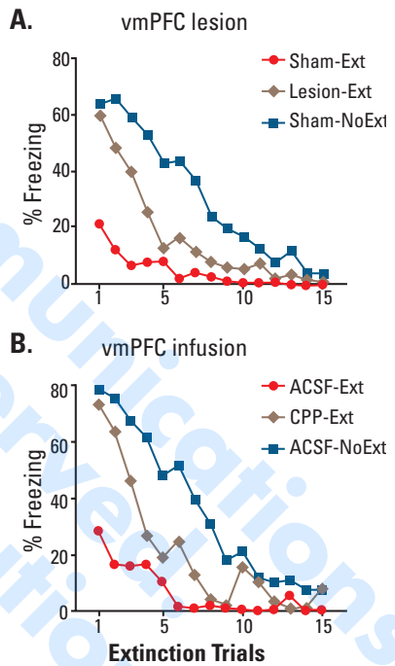
FIGURE 2.
Prefrontal extinction deficits are recall deficits, not storage deficits



Rats with vmPFC lesions (A) or NMDA receptor blockade in vmPFC (B) prior to extinction learning are unable to recall extinction, as indicated by high levels of fear, similar to no-extinction controls. Re-extinction in impaired rats, however, proceeded faster than in no-extinction controls. This "savings" in the rate of relearning suggests that extinction memory was present in lesioned/CPP groups, but could not be recalled. Thus, extinction is stored outside the vmPFC, but vmPFC is necessary for extinction recall.

(A) Adapted from Quirk GJ, Russo GK, Barron JL, Lebron K. The role of ventromedial prefrontal cortex in the recovery of extinguished fear. *J Neurosci.* 2000;20:6225-6231. Copyright (2000); (B) Adapted from Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ. Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. *Neuron.* In press. Copyright (2007).

NoExt=no extinction; Ext=extinction; ACSF=artificial cerebrospinal fluid; CPP=d(-)-3-(2-carboxypiperazine-4-yl)-propyl-1-phosphonic acid; vmPFC=ventromedial prefrontal cortex; NMDA=*N*-methyl-D-aspartate.

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The Ventromedial Prefrontal Cortex is Also Necessary for Expression of Conditioned Fear

Pre-training lesions of vmPFC have no effect on acquisition or expression of conditioned fear, consistent with the idea that the amygdala is sufficient for the acquisition and expression of conditioned fear. Permanent lesions, however, leave open the possibility that other areas of the brain can assume the role normally played by the lesioned structure.[44,45] To overcome this problem, Sierra-Mercado and colleagues[46] recently infused the sodium channel blocker tetrodotoxin into the vmPFC, to temporarily inactivate vmPFC neurons during specific phases of training. Consistent with lesion findings, inactivation of vmPFC prior to extinction learning disrupts extinction recall the following day. Unlike lesions, however, tetrodotoxin infusions into vmPFC decrease conditioned fear expression (Figure 3),[46,47] in agreement with other recent vmPFC inactivation results.[48,49] Freezing in the presence of a predator was unaffected by vmPFC inactivation, however, indicating that vmPFC inactivation does not simply disrupt rats' ability to freeze.[47] This suggests that activity in vmPFC neurons is necessary for expression of conditioned fear; the amygdala alone is not sufficient. However, vmPFC does not seem to be a site of plastic changes in fear conditioning, because pre-training inactivation does not prevent acquisition of fear conditioning.[46,47] Thus, vmPFC is a critical site of fear expression but not fear plasticity.

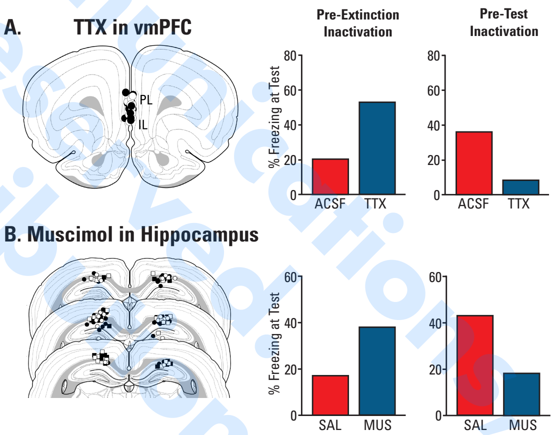
Pharmacologic inactivation revealed that vmPFC can both excite and inhibit fear expression. This property of vmPFC is supported by anatomical and physiological studies of vmPFC-amygdala connections. Whereas the infralimbic subregion projects mostly to inhibitory cells in the amygdala (see above), the prelimbic subregion projects to the basolateral and basomedial nuclei of the amygdala,[29,30] which are essential for the expression of conditioned fear.[45] Moreover, microstimulation of the prelimbic and infralimbic subregions increases and decreases, respectively, freezing in response to conditioned tones.[50] The ability of vmPFC to bidirectionally modulate amygdala activity highlights its role in regulating the expression of both fear and extinction.

THE HIPPOCAMPUS IS NECESSARY FOR CONTEXT-DEPENDENT RECALL OF EXTINCTION

If extinction retrieval is modulated by contexts, what is the neural mechanism by which this modulation occurs? Consistent with its established role in spatial processing,[51] the hippocampus has recently been implicated in contextual modulation of fear expression and extinction recall. As shown in Figure 3, hippocampal inactivation prior to extinction leads to deficient recall of extinction the following day.[52] However, inactivation of the dorsal hippocampus prior to extinction recall blocks the expression of fear outside the extinction context (ie, renewal).[13,53] These results suggest that the hippocampus uses contextual cues to help determine whether to recall fear or extinction during testing.[13]

The spontaneous recovery of fear indicates that extinction recall is subject to temporal factors in much the same way that it is subject to contextual factors. In fact, Bouton[14] has suggested that long gaps between extinction training and recall represent a shift in a "temporal context," thereby causing a renewal of fear.[54] Typically, the

FIGURE 3.
Pharmacologic inactivation of vmPFC and hippocampus has similar effects on fear expression



Pre-extinction inactivation of vmPFC (A) or hippocampus (B) leads to increased fear during testing, suggesting that these regions function together to enable extinction recall. In contrast, inactivation of either structure prior to testing causes decreased fear, suggesting that these regions function together to determine fear expression.

(A) Adapted from Sierra-Mercado D, Corcoran KA, Lebron K, Quirk GJ. Inactivation of ventromedial prefrontal cortex reduces expression of conditioned fear and impairs subsequent recall of extinction. *Eur J Neurosci.* 2006;24:1751-1758. Copyright (2006); (B) Adapted from Corcoran KA, Desmond TJ, Frey KA, Maren S. Hippocampal inactivation disrupts the acquisition and contextual encoding of fear extinction. *J Neurosci.* 2005;25:8978-8987. (Copyright 2005).

vmPFC=ventromedial prefrontal cortex; TTX=tetrodotoxin; PL=prelimbic subregion of the vmPFC; IL=infralimbic subregion of the vmPFC; SAL=saline; MUS=muscimol.

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passage of many days after extinction learning is required before there is a failure to recall extinction. However, interfering with vmPFC function accelerates this process, resulting in failure to recall extinction after only one day.[37,39]

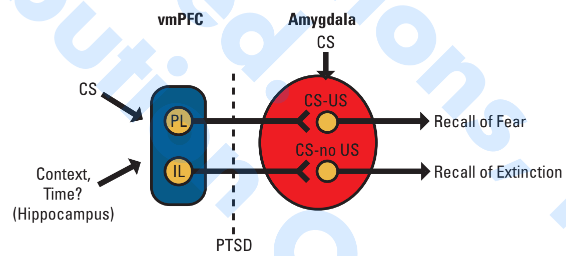
It is unknown how temporal factors interact with the neural circuits of extinction recall. Inactivation studies (Figure 3) suggest that hippocampal inputs to vmPFC are active soon after extinction training to regulate fear, but is there any evidence that the influence of the hippocampus on vmPFC changes over time? It has recently been shown that the passage of days causes memory for contextual fear conditioning to become less dependent on the hippocampus and more dependent on the vmPFC.[55] Thus, temporal delays may be encoded as shifts in activity from the hippocampus to vmPFC and other cortical regions during memory recall. If true, spontaneous recovery could be caused by biasing prefrontal recall mechanisms from the recall of extinction to the recall of fear, via time-dependent reorganization of hippocampal inputs.

HIPPOCAMPUS AND VENTROMEDIAL PREFRONTAL CORTEX WORKING TOGETHER?

Inactivation of hippocampus or vmPFC has similar effects on fear expression and extinction recall (Figure 3), suggesting that these two structures work together to mediate behavioral responses to conditioned stimuli. Indeed, the inability of vmPFC-impaired rats to retrieve extinction looks very much like fear renewal. Thus, vmPFC may be involved in mediating the effects of context on extinction retrieval, as previously suggested.[35,56,57] The hippocampus sends dense projections to vmPFC,[58-60] and hippocampus-vmPFC connections are potentiated by extinction training.[61] This pathway could, therefore, serve as a site of neural plasticity essential for extinction recall. Contrary to this hypothesis, Farinelli and colleagues[61] found that lesions of vmPFC did not prevent the modulation of extinction recall by potentiation of hippocampal outputs. As previously mentioned, lesions can lead to the recruitment of compensatory mechanisms. For example, direct hippocampo-amygdala projections could mediate the contextual modulation of extinction recall in lesioned rats.[56] Thus, lesions of vmPFC do not rule out a role for hippocampus-vmPFC interactions in mediating extinction recall in an intact animal. The activity of neurons in vmPFC is highly correlated with activity in hippocampal neurons,[62] and hippocampal stimulation gates the response of vmPFC neurons to other inputs.[63] Thus, activity in vmPFC may be regulated by the hippocampus in order to gate extinction recall under a variety of circumstances. We will be testing this hypothesis by recording neuronal activity in vmPFC in response to extinguished stimuli presented inside and outside the extinction context in rats with inactivated hippocampi.

Recent neuroimaging studies in humans support the idea that the vmPFC and hippocampus work together to recall extinction. Extinction training potentiates vmPFC activity, and this potentiation is correlated with recall of extinction.[64] Using a two-CS design, Milad and colleagues[65] observed that the hippocampus and vmPFC were both activated when subjects were recalling extinction versus conditioning. Similarly, Kalisch and colleagues[66] found that vmPFC and hippocampus were both activated when subjects were exposed to an extinguished CS in the extinction context, versus in the conditioning context. Therefore, the vmPFC and hippocampus seem to act together to mediate the effects of context on extinction recall in humans as well as in rats. The role of vmPFC and hippocampus in extinction recall is highlighted by volumetric studies of the brains of posttraumatic stress disorder (PTSD) patients, who have a smaller vmPFC and hippocampus

FIGURE 4.
Proposed model of the circuitry mediating extinction recall



The amygdala stores both conditioning (CS-US) and extinction (CS-no US) memories. CS information accesses both the amygdala and the vmPFC. In vmPFC, CS information is integrated with contextual and temporal information from the hippocampus in order to determine extinction recall. Outside the extinction context, vmPFC supports expression of the CS-US memory in the amygdala via projections from the prelimbic area. In the extinction context, vmPFC activates the inhibitory conditioned stimulus-'no unconditioned stimulus' memory via projections from the infralimbic area. In PTSD, loss of prefrontal modulation of amygdala (dashed line) would result in unrestricted recall of the CS-US fear memory.

vmPFC=ventromedial prefrontal cortex; CS=conditioned stimulus; PL=prelimbic subregion of the vmPFC; IL=infralimbic subregion of the vmPFC; US=unconditioned stimulus; PTSD=posttraumatic stress disorder.

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compared with non-PTSD controls.[67,68] As a result, traumatic stimuli lead to decreased vmPFC activation and increased amygdala activation in PTSD patients,[69,70] suggesting that PTSD reflects a loss of prefrontal control over the amygdala.

A MODEL AND CLINICAL IMPLICATIONS

The vmPFC lies at the center of a neurobiological network that mediates extinction recall (Figure 4). Information about the CS is transmitted to both the vmPFC and the amygdala. Contextual and temporal information surrounding CS presentation converges in vmPFC via hippocampal inputs. Using this additional information, vmPFC can support the expression of the CS-US memory through prelimbic projections, or support expression of the CS-"no US" extinction memory through infralimbic projections. Uncoupling vmPFC from the amygdala, such as occurs in PTSD (dotted line in Figure 4), removes the ability to regulate fear expression. Thus, CS activation of the amygdala would proceed unchecked.

By this logic, interventions that increase the coactivation of vmPFC and hippocampus should reduce the renewal of fear outside the extinction context. Willful cognitive adjustments, in which a patient evaluates emotional stimuli more positively, may improve extinction recall by enhancing vmPFC activity.[71,72] Pharmacologically enhancing metabolic activity[73] or NMDA receptor function[74,75] in vmPFC after extinction learning may also aid extinction recall.[76]

CONCLUSION

Through investigations of the neural circuitry underlying fear extinction, we have begun to uncover how psychological processes impact the ability to recall extinction. Evidence from fear conditioning studies in rats and humans suggests that vmPFC is necessary for extinction recall, and that coactivation of vmPFC and hippocampus may be necessary for the contextual regulation of extinction recall. The output of vmPFC can serve to either excite or inhibit the amygdala, thereby providing for bidirectional regulation of fear after extinction. Deficient function in this hippocampus-vmPFC extinction recall circuit is associated with disorders of fear and anxiety. Clinical treatments for fear and anxiety will continue to improve as we further define the neural basis of extinction recall. ***CNS***

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