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REVIEW

Retrieving fear memories, as time goes by…

FH Do Monte[1], GJ Quirk[1], B Li[2] and MA Penzo[3]

Research in fear conditioning has provided a comprehensive picture of the neuronal circuit underlying the formation of fear memories. In contrast, our understanding of the retrieval of fear memories is much more limited. This disparity may stem from the fact that fear memories are not rigid, but reorganize over time. To bring some clarity and raise awareness about the time-dependent dynamics of retrieval circuits, we review current evidence on the neuronal circuitry participating in fear memory retrieval at both early and late time points following auditory fear conditioning. We focus on the temporal recruitment of the paraventricular nucleus of the thalamus (PVT) for the retrieval and maintenance of fear memories. Finally, we speculate as to why retrieval circuits change with time, and consider the functional strategy of recruiting structures not previously considered as part of the retrieval circuit.

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INTRODUCTION

Animals have an extraordinary ability to associate threatening events with sensory stimuli (images, smells, sounds). Such memories can persist long after learning,[1–3] and this persistence is critical for survival.[4] The evolutionarily favored ability to remember cues that were previously associated with danger allows animals to select the most appropriate defensive responses.[5,6] Decades of research on 'fear (or threat) conditioning' have led to a comprehensive understanding of the neuronal circuitry controlling acquisition of fear memories (for recent reviews see refs 7–9), but much less is known about circuits for retrieval of these memories.

Part of the challenge in identifying fear retrieval circuits is that memories are not permanently stored into a single region, but gradually reorganize over time (for review see refs ,10–13). Recent studies in rodents provide evidence supporting a time-dependent reorganization of the fear retrieval circuits following both contextual fear conditioning,[14–23] as well as auditory fear conditioning.[24–29] However, a systematic comparison of the different circuits required for retrieval at early (hours after conditioning) vs late (days to weeks after conditioning) time points is lacking.

In this review, we summarize current evidence on the neuronal circuitry participating in the retrieval of auditory fear memories at early vs late time points. Prior reviews on the retrieval of auditory fear memories have focused largely on the 24-h post-conditioning time point, potentially missing temporal changes occurring in the retrieval circuits long after conditioning. We will begin by comparing lesion and pharmacological inactivation studies with more recent findings incorporating optogenetics, chemogenetics (mediated by designer receptors exclusively activated by designer drugs, DREADDs), and electrophysiological recordings from identified neurons *in vivo*. Next, we will discuss current literature surrounding the involvement of the paraventricular nucleus of the thalamus (PVT) in the regulation of fear memory. Finally, we speculate as to the functional significance of time-dependent alterations in retrieval circuits, and how current evidence discussed here could impact the design of future experiments in laboratory animals and humans.

FEAR MEMORY FORMATION: IMPORTANT CAVEATS

The process of fear memory formation is generally divided into three phases: acquisition, consolidation and retrieval. During the acquisition phase, learned associations between aversive outcomes and the cues that predict them (for example, contextual and auditory) are encoded in discrete brain circuits. Memory acquisition is then followed by a consolidation phase that lasts from a few hours (synaptic consolidation) to several days or even weeks (systems consolidation), allowing for encoded information to be stored as a memory trace. Learned fear associations can be assessed by measuring animals' display of defensive behaviors after learning, in a phase called fear memory retrieval. Because systems consolidation recruits multiple regions over time, brain circuits underlying memory retrieval can differ at early vs late time points.

Although the phases of fear memory formation are seemingly well defined, there are important caveats that need to be considered when interpreting behavioral studies using laboratory animals. For example, a systematic distinction between acquisition and consolidation phases may be difficult with some experimental designs. Indeed, in many cases, the effects of the pre-training manipulation extend beyond the training phase, and one cannot entirely rule out the possibility that the manipulation is also interfering with consolidation. The recent implementation of techniques with high temporal resolution (for example, optogenetics) have helped to circumvent this problem.[30] Similarly, in experiments using pre-retrieval inactivation of brain structures and/or selected circuitry, it may be particularly difficult to

[1]Laboratory of Fear Learning, Department of Psychiatry and Anatomy & Neurobiology, University of Puerto Rico School of Medicine, San Juan, Puerto Rico.; [2]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA and [3]Unit on the Neurobiology of Affective Memory, National Institute of Mental Health, Bethesda, MD, USA. Correspondence: Dr FH Do Monte, Laboratory of Fear Learning, Department of Psychiatry and Anatomy & Neurobiology, University of Puerto Rico School of Medicine, Ofc A231, 2nd Floor Main Building, San Juan 00935, Puerto Rico or Dr MA Penzo, Unit on the Neurobiology of Affective Memory, National Institute of Mental Health, 35 Convent Drive, Building 35 A Room 2E621, Bethesda, MD 20892, USA.
E-mail: fabriciodomonte@gmail.com or mario.penzo@nih.gov
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disentangle circuits of memory retrieval from those of memory storage. Although the observation of memory impairment during the test phase may suggest that a potential circuit is necessary for memory retrieval, it cannot determine if the same circuit is the specific site for memory storage.

Furthermore, a distinction between circuits of fear retrieval and fear expression may depend on whether specific behavioral comparisons are performed. For example, in fear conditioning, one may argue that a specific manipulation affects the retrieval, rather than the expression of fear responses, if the animal's ability to exhibit the same defensive response in a different behavioral protocol is preserved. This type of comparison has been demonstrated in a few studies where the ability to express fear responses was impaired during a conditioned fear test, but remained intact during an innate fear test.[31–33] Alternatively, evaluating fear memory in ways other than freezing behavior (for example, heart rate, blood pressure, avoidance and flight response) can also help to distinguish between retrieval and expression. In general, disambiguating retrieval and expression circuits can be complicated by the intermingled nature of circuits thought to control both processes.

Keeping in mind the abovementioned caveats, we will now review the target areas participating in early and late retrieval of fear memories.

EARLY RETRIEVAL OF FEAR MEMORIES

There is a general consensus that the acquisition of auditory fear memories requires the integration of sensory information in the amygdala (for review see refs 34,35). Specifically, information about tone and shock originating in cortical and thalamic areas converge onto principal neurons of the lateral nucleus of the amygdala (LA), leading to synaptic changes that store tone-shock associations.[36–39] Similar conditioning-induced changes in synaptic transmission have been recently reported in the lateral portion of the central nucleus of the amygdala (CeL),[40,41] an area that is also critical for fear memory formation.[42–44] In addition to their role in conditioning, LA and CeL are necessary for fear memory retrieval soon after conditioning (up to 24 h). A detailed description of the literature supporting these conclusions follows.

Amygdala microcircuits necessary for early retrieval

In the last decade, studies using lesions or pharmacological inactivation in rodents indicate that activity in the basolateral complex of the amygdala (BLA; comprising LA and the basal nucleus of the amygdala) is critical for retrieval of fear memory 24 h following conditioning.[45–48] LA neurons project to CeL, as well as to the basal nucleus of the amygdala (BA), both of which are connected with the medial portion of the central nucleus of the amygdala (CeM).[49–53] Neurons in CeM then project to downstream regions, such as the periaqueductal gray and the hypothalamus, to mediate autonomic and behavioral correlates of conditioned fear.[54,55] Tone-evoked responses in LA neurons are increased within 1 h following fear conditioning,[56,57] and persist for several days after learning.[58–60] Similar conditioned responses 24 h after conditioning have been demonstrated in BA,[61,62] and inactivating BA at this time point impairs fear retrieval.[45,61] BA contains a population of glutamatergic neurons in which activity is correlated with fear expression ('fear neurons'), and participate in the generation of fear responses by relaying LA activity to the CeM.[8,62]

Similar to BA, retrieval of fear memories at the 24 h time point activates neurons in CeM, and pharmacological inactivation of CeM with the $GABA_A$ agonist muscimol impairs fear retrieval.[44,63] In contrast to CeM, muscimol inactivation of CeL promotes freezing behavior,[44] consistent with inhibitory control of CeM by CeL. In fact, it has been suggested that the release of CeL-mediated inhibition in CeM is critical for the expression of freezing during retrieval of fear memory.[41,44,64] This disinhibition hypothesis is also supported by electrophysiological findings of two populations of inhibitory neurons in CeL 24 h following fear conditioning: one with excitatory tone responses (CeL_{ON} neurons), and another with inhibitory tone responses (CeL_{OFF} neurons).[44] A fraction of CeL_{OFF} neurons expresses protein kinase C-delta, projects to CeM, and is hypothesized to tonically inhibit CeM neurons.[44,64] CeL_{ON} neurons, which likely do not overlap with protein kinase C-delta positive neurons,[64] selectively inhibit their CeL_{OFF} counterpart leading to the disinhibition of CeM output neurons during fear memory retrieval.[44,64]

There also exists a functional dichotomy within CeL based on the discordant expression of the neuropeptide somatostatin (SOM; CeL-SOM^+ neurons and CeL-SOM^- neurons). Whereas optogenetic silencing of CeL-SOM^+ neurons impairs fear memory retrieval, optogenetic activation of CeL-SOM^+ neurons induces fear responses in naïve mice.[41] Further, experiments are necessary to determine if CeL-SOM^+ neurons overlap with CeL_{ON} neurons. A similar disinhibitory mechanism has been described in the amygdala for the medial intercalated cells, a group of GABAergic cells located in the intermediate capsule of the amygdala between BLA and central nucleus of amygdala (CeA).[65–67] During early fear retrieval, excitatory inputs from LA neurons excite the dorsal portion of medial intercalated cells generating feed-forward inhibition of their ventral portion. The reduction in activity in the ventral portion of medial intercalated cells release CeM output neurons from inhibition, thereby allowing fear responses to occur (for review see ref. 8).

Early retrieval requires the prelimbic cortex

The medial prefrontal cortex (mPFC) has long been suspected of regulating emotional responses in animals and humans.[68–72] Two subregions of the rodent mPFC, the prelimbic cortex (PL) and the infralimbic cortex, have emerged as opposites in the regulation of fear memories. Whereas PL activity is necessary for fear retrieval soon (24 h) after conditioning,[28,31,47] infralimbic cortex activity at this same time point is critical for fear extinction learning.[73–77]

A significant fraction of PL neurons (~25%) displays increased and sustained tone-evoked firing 24 h after conditioning, a response that mirrors the time course of freezing behavior.[78,79] In this way, PL activity predicts the magnitude of fear responses.[80,81] Conditioned responses of PL neurons depend on BLA inputs, as pharmacological inactivation of BLA decreases both spontaneous activity and tone responses in putative PL projection neurons.[82] Consistent with this idea, a recent study combining retrograde tracing with optogenetic techniques demonstrated that 'fear neurons' of BA project exclusively to PL, and optogenetic silencing of these projections 24 h after conditioning inhibits fear retrieval.[83]

PL not only receives projections from BLA, but also projects to this region.[84,85] Silencing of PL projections to BLA with optogenetic techniques 6 h after conditioning impaired fear memory retrieval,[28] suggesting that PL exerts a top–down modulation of amygdala activity. Consistent with this idea, retrieval of conditioned fear at 24 h after conditioning is correlated with synchronous 4 Hz oscillations in the PL-BLA circuits, and optogenetic generation of 4 Hz oscillations in PL is sufficient to elicit freezing responses in naïve mice.[81] Conditioned increases in PL activity may involve disinhibition, as it was recently shown that PL interneurons expressing parvalbumin (PV^+) decrease their activity after conditioning, and optogenetic silencing of these cells drives fear responses.[86] Although these findings suggest a critical role of PL interneurons in fear expression, further studies are needed to investigate if the recently described long-range GABAergic neurons in mPFC[87] can also contribute to fear memory regulation.[88]

LATE RETRIEVAL OF FEAR MEMORIES

A growing number of studies indicate that circuits guiding the retrieval of fear memories change with the passage of time after conditioning (see Figure 1). Below, we review the evidence supporting a time-dependent reorganization of the fear circuits, beginning with the auditory cortex, a region necessary for retrieval at late, but not early, time points.

Recruitment of auditory cortex for retrieval

Fear conditioning induces increased tone-evoked firing in the primary auditory cortex neurons 1–4 h after learning.[89] Because the latency of conditioned tone responses in the auditory cortex (~20–40 ms) is longer than in LA (~10–20 ms),[57] one can conclude that LA tone responses assessed early after conditioning do not depend on auditory cortex inputs. Consistent with this, lesions of the primary auditory cortex shortly before or after fear conditioning do not prevent the acquisition or consolidation of fear memories, suggesting that the auditory thalamus is sufficient to support fear learning in the amygdala[90–93] (but see ref. 94). Instead, activity in the primary auditory cortex seems to be critical for fear memory acquisition under special training conditions such as the use of complex tone sequences[95] or a gap between the tone and the unconditioned stimulus (trace fear conditioning).[96,97]

Whereas the primary auditory cortex seems to be dispensable for the formation of classical auditory fear conditioning, the secondary auditory cortex (Te2) has a critical role in the retrieval of fear memory long after conditioning.[25,27] Lesions of Te2 performed 30 days, but not 24 h, after conditioning impair fear retrieval,[27] and conditioning increases the expression of the neuronal activity marker *zif*268 in Te2 30 d after, but not 24 h after, learning.[25,27] Interestingly, pharmacological inactivation of Te2 at 24 h after conditioning impaired fear retrieval 30 days, but not 7 days after conditioning, suggesting that early activity in Te2 neurons is required for the formation of older fear memories.[98] Together, these results highlight a putative role for the auditory cortex in the retrieval of fearful stimuli long after fear associations are established.[99]

The recruitment of area Te2 for retrieval of auditory fear memory resembles the time-dependent recruitment of the anterior cingulate cortex (aCC) for retrieval of contextual fear memory.[13] Retrieval of contextual fear information 24 h after conditioning depends on activity in the hippocampus, but not in the aCC, whereas retrieval 36 days after conditioning depends on activity in the aCC, but not in the hippocampus.[16] Retrieval of fear memories at 24 h or 36 days was associated with an increase in dendritic spine density in the hippocampus or the aCC, respectively.[21] Interestingly, blocking spine growth in the aCC during the first post-conditioning week disrupts memory consolidation.[100] Although these studies suggests a cellular mechanism underlying the time-dependent involvement of the hippocampus and aCC in contextual fear retrieval, whether the Te2 region also undergoes temporal plasticity changes following auditory fear conditioning remains to be determined. For additional information about the temporal reorganization of hippocampus-dependent memories, the readers are encouraged to read other reviews.[101–104]

Shifting of retrieval circuits in the prelimbic cortex

Prior studies have demonstrated that cortical areas are necessary for retrieval at late but not early time points. This raises the question as to the mechanisms involved in the transitions of circuits across time. An important clue comes from PL, a structure previously shown to be necessary for 24 h retrieval.[28,31,47,86] A recent study demonstrated that PL is necessary for retrieval of fear at both 6 h and 7 days after conditioning, but the target of PL efferent fibers shifts across the two time points.[28] PL neurons projecting to BLA are necessary for retrieval at 6 h (but not 7 days), whereas PL neurons projecting to the PVT are required for retrieval at 7 d (but not 6 h) following conditioning. This time-dependent shift between retrieval circuits likely involves different populations of neurons in the PL, because neurons projecting to BLA or PVT are located in different layers of PL.[28,85,105,106] Although further studies on PL circuit dynamics are needed, these findings suggest that time-dependent changes in PL efferents may serve to reorganize retrieval circuits in subcortical targets.

The role of the basolateral amygdala in late retrieval

The BLA has been classically described as a critical region for the retrieval of recently acquired fear memories. However, its role in fear memory retrieval long after conditioning is far less clear, with evidence either in support of or against its involvement.

Studies in rats have demonstrated that retrieval of fear memory 28 days after conditioning increases the expression of the neuronal activity marker *zif*268 in LA,[25,27] with no significant changes in BA.[27] Fear retrieval at 28 days is also correlated with increased coherence between the BLA and the auditory cortex (Te2) in the low-theta activity (3–7 Hz),[107] a frequency range that has been associated with freezing responses.[108] Evidence supporting the necessity of BLA in fear memory retrieval at late time points comes from experiments using post-training lesion techniques in rodents. Indeed, excitotoxic lesions of BLA performed before,[109] as well as 7 days, 14 days or 16 months after fear conditioning produced significant deficits in fear retrieval,[3,110] suggesting that BLA is an important substrate to retrieve old fear memories. In contrast, studies in monkeys have demonstrated that lesions of the amygdala, including BLA, impair the acquisition of fear memories, but not retrieval when performed 14–45 days after conditioning.[111,112] Nevertheless, because lesion techniques provide an inaccurate control of the lesion size, it is difficult to determine whether these effects are due to damage to adjacent areas (for example, CeA and the intercalated cells).

In contrast to lesion studies, recent reports employing newer methodologies have challenged the idea that BLA is a critical site for the retrieval of fear memories several days after conditioning. Inducible silencing of synaptic output from BLA neurons performed 3 days after fear acquisition had no effect on fear retrieval, suggesting that BLA is dispensable for fear memory retrieval long after conditioning.[113,114] Further evidence that BLA activity is not required for late fear memory retrieval is the observation that optogenetic silencing of either BLA neurons or PL-BLA communication impaired the retrieval of 6 h-old, but not 7-day-old fear memories.[28] Consistent with this, BLA neurons showed increased expression of the neuronal activity marker cFos during fear retrieval at 6 h or 24 h after conditioning, but not 7 days after conditioning.[28] Studies using the inhibitory avoidance paradigm have also suggested that BLA activity is temporarily required following conditioning, being critical for the retrieval of recent (1 day), but not older (>10 days) fear memories.[115–118]

Altogether, there is increasing evidence that although BLA participates in the acquisition and early retrieval of fear memories, late retrieval of fear memories may occur independently of BLA. A time-limited role of BLA neurons in memory retrieval may increase the availability of BLA neurons for new associations, with more permanent storage of emotional memories occurring in cortical structures (for example, mPFC) where contextual and emotional information are integrated with circuits involved in decision-making[119] (discussed later in this review). Although the mechanisms by which fear memories are transferred from BLA remain unclear, the neuronal circuit underlying the retrieval of fear memories downstream of the mPFC seems to require a previously overlooked structure, the PVT.

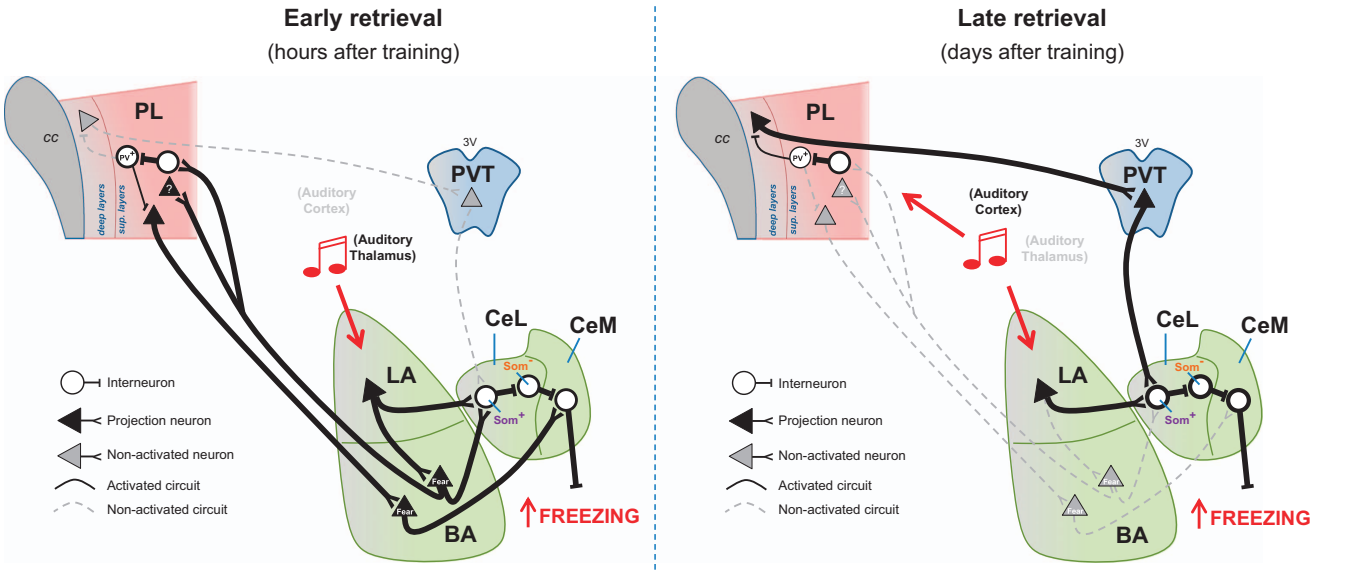

Figure 1. Temporal reorganization of the circuits necessary for retrieval of auditory fear memories. Left – retrieval of fear memories at early time points after conditioning recruits reciprocal activity between the amygdala and PL. During early retrieval, the conditioned tone activates auditory thalamus inputs to LA. Increased activity in LA neurons activates SOM+ neurons in CeL, thereby disinhibiting CeM output neurons that mediate fear responses. Increased activity in LA neurons also activates BA neurons interconnected with PL, thereby allowing a top–down control of fear retrieval. Right – retrieval of fear memories at late time points after conditioning recruits activity in PL neurons projecting to PVT, as well as PVT neurons projecting to CeL. During late retrieval, the conditioned tone activates auditory cortex inputs to both LA and PL. Increased activity in PL interneurons inhibits PV^+ interneurons, thereby disinhibiting PL neurons projecting to PVT. Increased activity in PVT neurons activates SOM+ neurons in CeL, and consequently disinhibits CeM output neurons that mediate fear responses. BA, basal amygdala; cc, corpus callosum; CeL, lateral portion of the central amygdala; CeM, medial portion of the central amygdala; LA, lateral amygdala; PL, prelimbic cortex; PVT, paraventricular nucleus of the thalamus; PV^+, parvalbumin positive neurons; SOM+, somastotatin positive neurons; SOM–, somatostatin negative neurons; 3 V, third ventricle.

Paraventricular nucleus of the thalamus is recruited for retrieval

The PVT is a subdivision of the dorsal midline thalamus that is anatomically connected with multiple brain regions known to be involved in fear regulation, including PL, infralimbic cortex, BLA, CeA and periaqueductal gray.[105,120–123] A role of PVT in fear retrieval at the 24 h time point has been suggested by previous studies using lesion or pharmacological inactivation.[124,125] Extending these findings, a recent study using chemogenetic techniques in mice demonstrated that PVT projections to CeL are essential for fear memory consolidation, as well as for the retrieval of fear memory at the 24 h time point.[29] A parallel study combining pharmacological inactivation and optogenetic techniques in rats demonstrated that, following conditioning, PVT becomes increasingly necessary for fear memory retrieval.[28] Unlike BLA, PVT is not required for retrieval 6 h after conditioning, but is required at 24 h and thereafter. Pharmacological inactivation of PVT at late time points (tested at 7 and 28 days) also impaired retrieval in a subsequent drug-free session, suggesting that activity in PVT neurons is necessary for the maintenance of fear memory.[28]

These recent findings argue for PVT as an important regulator of fear memories, becoming critical for fear memory retrieval 24 h after conditioning, and raise the following questions: (1) When does PVT become recruited into the fear memory circuit? (2) How does PVT regulate fear memories? and (3) What are the advantages of PVT recruitment? In the following sections, we will discuss current evidence that may help to answer some of these questions and also identify the critical experiments needed to fill the knowledge gap.

WHEN IS PVT RECRUITED INTO THE FEAR CIRCUIT?

Both immunohistochemical and electrophysiological evidence support the notion that PVT is activated early after fear conditioning. PVT displays a significant increase in cFos protein expression immediately after conditioning,[29] and a fraction of PVT neurons shows increased spontaneous firing rate 2-h post conditioning.[28] However, transient pharmacological inactivation of the dorsal midline thalamus, including PVT, immediately before conditioning had no effect on fear memory retrieval assessed 24 h later.[124] This is in contrast with the observation that pre-conditioning chemogenetic inhibition of CeL-projecting PVT neurons impairs fear memory when tested at 24 h.[29] The discrepancy between these two studies may be accounted for by the difference in temporal dynamics of the two manipulations. Whereas pharmacological inactivation with muscimol is expected to last 2–3 h following infusion,[126] chemogenetic inhibition is known to have a more lasting effect (~10 h).[127] Thus, although muscimol inactivation of PVT is expected to be restricted to acquisition-related processes, chemogenetic silencing could potentially interfere with consolidation processes including the shifting of circuits. Indeed, the difference between these findings suggests that recruitment of PVT may occur sometime between 3 and 10 h after conditioning, although additional experiments are needed.

In agreement with the previous explanation, chemogenetic inhibition of PVT neurons before fear conditioning does not affect conditioning-induced synaptic plasticity onto SOM^+ CeL neurons – a recently identified cellular process critical for fear memory formation[41] – at 3 h following conditioning.[29] Nonetheless, the same manipulation does impair this CeL plasticity when assessed at 24 h following conditioning.[29] These results suggest that ongoing PVT activity following conditioning is required for the consolidation of CeL plasticity. However, to directly test the hypothesis that the PVT-CeL pathway is involved in fear memory consolidation, one would like to selectively inhibit CeL-projecting PVT neurons for an extended period of time starting immediately after conditioning.

Consistent with the hypothesis that PVT is recruited for fear retrieval, the proportion of PVT neurons showing either increased tone responses or changes in spontaneous firing rate increases significantly from 2 to 24 h post-conditioning.[28] These observations highlight PVT's importance for the maintenance, albeit not for the induction, of fear-evoked synaptic plasticity; although a potential role of PVT in the acquisition of other types of fear learning including associative blocking[128] and habituation[129] has been recently reported. Together with the finding that PVT becomes critical for fear memory retrieval 24 h, but not 6 h, after conditioning,[28,29] current evidence indicates that PVT regulates both the long-term retrieval and maintenance of fear memory. In contrast, various features of short-term memory such as fear-induced synaptic plasticity (3 h) and fear retrieval (6 h) appear to be PVT-independent.

Another important question regarding the time-dependent recruitment of PVT is whether PVT neurons activated early on following fear conditioning are different from those activated later when PVT becomes critical for fear memory retrieval and maintenance. A partial answer to this question may be found in the observation that PVT neurons displaying tone responses 2 h after conditioning are distinct from those neurons displaying tone responses 24 h after conditioning.[28] Nevertheless, to fully address this question, one would need to systematically compare large populations of PVT neurons that are activated by fear memory retrieval at early vs late time points. Currently, a wide range of novel experimental approaches, including calcium and/or voltage imaging of identified neuronal ensembles in behaving animals, would help to tackle this issue.[130,131]

THE PVT-AMYGDALA CIRCUIT IN FEAR MEMORY REGULATION

Although moderate projections from PVT are found in multiple amygdala nuclei, CeL is the main amygdala recipient of PVT efferent fibers.[120,121,123] Rats with PVT lesions exhibit a significant increase in stress-induced cFos expression in the CeL.[132] Similarly, increased cFos expression was observed in CeL when PVT was inactivated during a fear retrieval session,[124] suggesting that PVT normally serves to suppress the recruitment of CeL neurons. CeL inhibition is currently thought to be a critical step in the retrieval of fear memories,[44,64] raising the possibility that PVT may control fear memory retrieval by promoting CeL inhibition. However, such inhibition is unlikely a result of inhibitory projections from PVT, as the midline thalamus is largely devoid of GABAergic neurons[133–135] (but see ref. 136).

A closer look at the PVT-CeL microcircuit in mice reveals that PVT projections preferentially target SOM^+ neurons of CeL, and enhance their excitability.[29] In addition, optogenetic activation of PVT afferents in CeL causes indirect inhibition of SOM^- neurons,[29] consistent with previous observations that SOM^+ CeL neurons are powerful local inhibitors.[41] Thus, activation of SOM^+ neurons could be the mechanism by which PVT promotes CeL local inhibition and thereby fear retrieval. However, the cellular and molecular mechanisms underlying PVT's role in fear memory consolidation and maintenance are far less clear. A potential answer may be found in the observation that the brain-derived neurotrophic factor (BDNF) mediates PVT-CeL communication.[29]

BDNF is a critical regulator of neuronal plasticity and synaptic function,[137,138] and has been heavily implicated in memory formation.[139] In the fear circuit, BDNF regulates both fear learning in the BLA[140,141] and fear extinction in the mPFC.[142,143] A pivotal role of BDNF has also been reported for the persistence of fear memories,[144,145] suggesting that BDNF signaling in PVT-CeL may be a potential candidate to mediate the maintenance of fear memories. Indeed, BDNF-mediated communication between PVT and CeL neurons is critical for both fear learning and the long-term expression of fear-induced CeL synaptic plasticity.[29] In addition, because BDNF mediates PVT-CeL neurotransmission, BDNF may subserve PVT's function in fear memory maintenance, although direct evidence for this is still lacking.

As previously mentioned, inactivation of PVT inputs to the CeA during a 7-day fear memory retrieval session impairs the subsequent retrieval of fear memory 1 day later.[28] This observation is consistent with the idea that PVT-CeA communication is essential for the re-consolidation of fear memory. Surprisingly, however, fear memory re-consolidation is not impaired by intra-PVT blockade of protein synthesis or mitogen-activated protein (MAP) kinase signaling,[28,146] both critical mediators of neuronal plasticity.[147] A possible explanation for this finding is that, although PVT may participate in the maintenance and/or re-consolidation of fear memory within the amygdala, it may not be a site of plasticity itself. Nevertheless, increased expression of MAP kinase in the PVT has been associated with impaired retention of extinction memories in adolescent rats.[148] Activation of MAP kinase signaling in PVT may strengthen the formation of fear memories, leading to impaired retrieval of extinction memories during adolescence.

The observation that interfering with either protein synthesis or MAP kinase activity in the PVT does not affect memory maintenance argues against the idea that PVT stores fear memory. Instead, long-term storage for fear memories may be found in cortical structures, in particular the mPFC as proposed by others.[13,16,119,149] However, why mPFC differentially recruits BLA and PVT at early vs late time points, respectively, remains unclear. In the following section we attempt to bring clarity to this issue by highlighting several known functional distinctions between BLA and PVT.

WHAT ARE THE ADVANTAGES OF RECRUITING PVT INTO THE FEAR CIRCUIT?

Anatomical studies have demonstrated that PVT is reciprocally interconnected with multiple limbic, hypothalamic and cortical regions, including the mPFC.[105,120,121,150] Current understanding of the functional role of PVT is mainly based on lesion studies, which placed PVT as part of the brain circuitry controlling both arousal mediated by negative states and adaptive responses to stress (for review see refs 151,152). PVT receives dense inputs from the locus coeruleus (noradrenergic)[153] and the lateral hypothalamus (orexinergic),[105] both regions (and neurotransmitters) directly implicated in the control of arousal.[154] Studies in rodents have shown that PVT is activated by a variety of physical and psychological stressors including restraint,[155,156] foot shock,[157] sleep deprivation[158] and forced swim.[159,160] In turn, PVT activity has been shown to modulate neuroendocrine,[161,162] autonomic[155,163] and behavioral responses to stress.[164] Together, these studies suggest that recruitment of PVT during the establishment of long-term fear memories may serve to coordinate adaptive responses to stress.

Consistent with this, functional impairments in PVT have been implicated in maladaptive stress responses such as increased vulnerability to stress, exacerbated anxiety phenotypes and depressive-like behaviors such as despair, anhedonia and lack of motivation.[151,165] Notably, pharmacological activation of PVT produces anxiety and fear-like behavior in rats,[166,167] and increased activity in PVT neurons projecting to the CeA is correlated with depressive-like behavior in rats,[160] reinforcing the idea that dysfunction in PVT circuits may lead to the maladaptive expression of fear and/or aversive behaviors.

Recent evidence has also implicated PVT in the development of drug-seeking and addiction-related behaviors,[168] suggesting that dysfunction of this thalamic subregion may be involved in inappropriate retrieval of reward-associated memories. PVT's involvement in the modulation of maladaptive forms of both aversive and reward processes is intriguing, given that there is a high comorbidity between mood, anxiety and addiction disorders

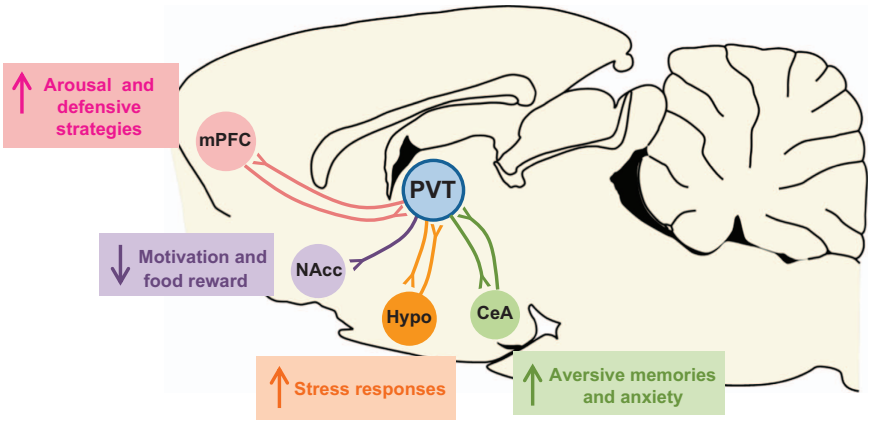

Figure 2. Recruitment of PVT into the fear circuit may serve to integrate defensive behaviors with adaptive biological responses. The PVT is reciprocally interconnected with the mPFC, the Hypo and the CeA. In addition, PVT is the major source of inputs to the NAcc. This pattern of anatomical connections places PVT in a central position to integrate negative emotional memories with adaptive biological responses such as arousal and goal-directed behaviors (through connections with the mPFC), control of food intake (through projections to the NAcc), regulation of circadian rhythms and stress-adaptation (through connections with the hypothalamus). CeA, the central nucleus of the amygdala; Hypo, hypothalamus; mPFC, medial prefrontal cortex; NAcc, nucleus accumbens; PVT, paraventricular nucleus of the thalamus.

in humans.[169] However, it remains to be determined whether a link exists between PVT dysfunction and the co-expression of these pathological phenotypes.

Consistent with the idea of coordinating both positive and negative emotional states, PVT is activated by cues associated with either food[170,171] or drug reward,[172–174] as well as by cues associated with aversive taste[175] or fearful stimuli.[28,175,176] PVT sends dense glutamatergic projections to the nucleus accumbens (NAcc),[120,177] a region implicated in the regulation of reward-seeking behavior.[178] Activity in PVT neurons projecting to the NAcc is correlated with reinstatement of alcohol-seeking behavior in rats,[179] and inactivation of PVT-NAcc projections using either an optogenetic or a chemogenetic approach attenuates the aversive symptoms induced by morphine withdrawal in mice.[177] Thus, PVT efferents to NAcc seem to be implicated in the aversive outcome induced by the absence of reward. In summary, current studies indicate that PVT is involved in the regulation of stress-related behaviors with CeA-projecting neurons of PVT driving fear-induced defensive responses (as discussed above), and NAcc-projecting neurons driving withdrawal-induced drug-seeking behavior.[177,179,180]

Similar to PVT, the BLA has also been implicated in the control of both fear- and reward-associated behaviors.[181,182] However, whereas BLA's participation in fear- and reward-associated behaviors involves a general role in Pavlovian associative learning,[183,184] PVT's participation in these processes implicates the coordination of multiple adaptive functions in response to stress, including the regulation of circadian rhythms, core temperature and energy balance.[155,163,185] Thus, recruitment of PVT into the retrieval circuit may serve to integrate fear-associated memories with other adaptive functions that control homeostasis (Figure 2). For instance, PVT is bidirectionally connected with the suprachiasmatic nucleus (SCN) of the hypothalamus,[121,186,187] the master circadian pacemaker of the mammalian brain.[188] Notably, PVT displays diurnal variations in neuronal activity,[189,190] and lesions of PVT abolish light-induced phase shifts in circadian rhythmicity.[185] Thus, unlike BLA which lacks a direct connection with the SCN,[191] PVT can regulate circadian rhythms by modulating the activity of SCN neurons,[192] aside from conveying circadian information from the SCN to other brain regions including the mPFC, the NAcc and other amygdala nuclei.[163]

In addition to the proposed model binding PVT to the integration of stress-related phenotypes, evidence indicate a more specific role for PVT in controlling susceptibility to stress.[155,164,193] PVT modulates the behavioral and neuroendocrine responses to a novel stressor following chronic stress,[161,194] and has been referred to as a potential 'stress-memory' center of the brain.[164,193] Therefore, unlike BLA, which orchestrates the formation of associative memories, PVT may serve to control the magnitude of adaptive and/or maladaptive behaviors in response to stress. Consistent with this hypothesis, a positive correlation has been observed between the duration of immobility in the forced swim test and the activation of CeA-projecting PVT neurons.[160] In addition, direct infusion of BDNF (which mediates PVT-CeA communication) into the CeA before fear conditioning, enhances cue-evoked fear expression the following day.[29] These results suggest that PVT may control the magnitude of both fear and depressive-like behaviors through a circuit dedicated to stress sensitivity. Within this context, mPFC's recruitment of PVT could allow the integration of threat prediction with the subject's prior stress history to dictate behavioral outcome.

CONCLUSIONS

The studies reviewed here support the idea that the circuits mediating the retrieval of fear memories change with the passage of time following conditioning. We speculate that such reorganization of fear retrieval circuits may serve various functions, including: (1) integration of fear memories with other adaptive responses, via recruitment of PVT; (2) strengthening of fear memories by increasing BDNF release from PVT to the CeL neurons; (3) increasing the availability of BLA neurons for future associations by detaching BLA neurons from the circuits necessary for retrieval of long-term fear memories. Possible benefits of time-dependent reorganization of retrieval circuits have been previously suggested with respect to hippocampal-dependent memories.[195,196] Memories progress from hippocampal to extra-hippocampal structures to either become more schematized[195] or to avoid interference with previous existing information,[196] two hypotheses that could also be contemplated for hippocampal-independent memories.

Although much remains to be discovered regarding the mechanisms mediating the reorganization of retrieval circuits, the present findings emphasize the importance of investigating, at the molecular, cellular and circuit levels, how aversive memories are retrieved across time. Prior studies of retrieval circuits have

focused on the 24 h post-conditioning time point. Understanding the time-dependent restructuring of fear retrieval circuits may be relevant to the treatment of post-traumatic stress disorder, given that these patients seek medical assistance weeks or even months after the initial trauma.[197] The advance of optogenetic tools, combined with calcium imaging and recording from identified neurons, provides a unique opportunity to understand the temporal dynamic of memory reorganization. In addition, human imaging studies focusing on the temporal modifications of retrieval circuits may inform us as to how aversive memories persist over time, providing alternative targets for pharmacological treatment in patients with anxiety disorders.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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