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Retrieving fear memories, as time goes by…

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Abstract

Fear conditioning researches have led to a comprehensive picture of the neuronal circuit underlying the formation of fear memories. In contrast, knowledge about 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 clarity and raise awareness on 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 after conditioning. We focus on the temporal recruitment of the paraventricular nucleus of the thalamus, and its BDNFergic efferents to the central nucleus of the amygdala, for the retrieval and maintenance of fear memories. Finally, we speculate as to why retrieval circuits change across time, and the functional benefits of recruiting structures such as the paraventricular nucleus into the retrieval circuit.

Keywords

Paraventricular thalamus; amygdala; prefrontal cortex; long-term memory; BDNF

INTRODUCTION

Animals have an extraordinary ability to associate threatening events with sensory stimuli (e.g., images, smells or sounds). Such memories can persist long after learning[1–3], and this persistence is critical for survival[4]. This evolutionary 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 conditioning” have led to a comprehensive understanding of the neuronal circuitry controlling acquisition of fear memories (for recent reviews see:[7, 8, 9]), but much less is known about circuits for retrieval of these memories.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

Part of the challenge in identifying fear retrieval circuits is that memories are not permanently stored into a single region, but are gradually reorganized over time (for review see:[10, 11–13]). Recent studies in rodents provide evidence supporting a time-dependent reorganization of the fear retrieval circuits following both contextual fear conditioning[14–22], as well as auditory fear conditioning[23–28]. However, a systematic comparison of the different circuits required during early (hours after conditioning) and late (days to weeks after conditioning) retrieval of fear memories 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-hour 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. Next, we will speculate on the functional significance of alterations in retrieval circuits, and how current evidence discussed here could impact the design of future experiments in both laboratory animals and humans.

Early retrieval of fear memories

Before discussing the circuits that mediate the retrieval of fear memories, it is important to review the target areas participating in the acquisition 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:[29, 30]). 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[31–34]. Similar conditioning-induced changes in synaptic transmission have been recently reported in the lateral portion of the central nucleus of the amygdala[35, 36], an area that is also critical for fear memory formation[37–39]. In addition to their role in conditioning, LA and CeL are necessary for fear memory retrieval soon after conditioning (up to 24 h). We will discuss this in detail in the following sections.

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[40–43]. 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[44–48]. Neurons in CeM then project to downstream regions, such as the periaqueductal gray (PAG) and the hypothalamus, to mediate autonomic and behavioral correlates of conditioned fear[49, 50]. Tone-evoked responses in LA neurons are increased within one hour following fear conditioning[51, 52], and persist for several days after learning[53–55]. Similar conditioned responses 24 h after conditioning have been demonstrated in BA[56, 57], and inactivating BA at this time point impairs fear retrieval[40, 56]. 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, 57].

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[39, 58]. In contrast to CeM, muscimol inactivation of CeL promotes freezing behavior[39], 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[36, 39, 59]. This disinhibition hypothesis is also supported by electrophysiological findings showing two populations of inhibitory neurons in CeL 24 h following fear conditioning: one exhibiting excitatory tone responses (CeL_{ON} neurons), and another exhibiting inhibitory tone responses (CeL_{OFF} neurons)[39]. The CeL_{OFF} neurons, a fraction of which can be accounted for by their expression of protein kinase C-delta, project to CeM and are hypothesized to drive the tonic inhibition of CeM neurons[39, 59]. CeL_{ON} neurons selectively inhibit their CeL_{OFF} counterpart, which presumably leads to the disinhibition of CeM output neurons during fear memory retrieval.

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[36]. Additional 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 (mITCs), a group of GABAergic cells located in the intermediate capsule of the amygdala between BLA and central nucleus of amygdala (CeA)[60–62]. During early fear retrieval, excitatory inputs from LA neurons excite the dorsal portion of mITCs generating a feed-forward inhibition of their ventral portion. The reduction in activity in the ventral portion of mITCs release CeM output neurons from inhibition, thereby allowing fear responses to occur (for review see:[8])

Early retrieval requires the prelimbic cortex—The medial prefrontal cortex (mPFC) has long been suspected of regulating emotional responses in animals and humans[63–65]. Two subregions of the rodent mPFC, the prelimbic cortex (PL) and the infralimbic cortex (IL), have emerged as being antagonistic to each other in the regulation of fear memories. Whereas PL activity is necessary for fear retrieval soon (24 h) after conditioning[27, 42, 66], IL activity at this same time point is critical for fear extinction learning [67–69].

PL neurons display increased tone-evoked firing 24 h after conditioning, which mirror the time course of freezing behavior[70, 71]. In this way, PL activity predicts the magnitude of fear responses[72]. Conditioned responses of PL neurons depend on BLA inputs, as pharmacological inactivation of BLA decreased both spontaneous activity and tone responses in putative PL projection neurons[73]. 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[74].

Previous neuroanatomical studies have demonstrated that PL not only receives projections from BLA, but also projects to this region[75, 76]. Silencing of PL projections to BLA with optogenetic techniques 6 h after conditioning impaired fear memory retrieval[27], suggesting that PL exerts a top-down modulation of amygdala activity during fear retrieval soon after conditioning. 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 augments fear responses[77]. While these findings suggest a critical role of PL interneurons in fear retrieval, further studies are needed to investigate if the recently described long-range GABAergic neurons in mPFC[78] can also contribute to fear memory regulation[79].

Later 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. Below, we review the evidence supporting a time-dependent reorganization of the fear circuits, beginning with the auditory cortex, a region that is completely dispensable at early time points, but becomes essential at late time points.

Recruitment of auditory cortex for retrieval—Lesions of the auditory cortex shortly before or after fear conditioning do not prevent the acquisition or consolidation or fear memories, suggesting that the auditory thalamus is sufficient to support fear learning in the amygdala[80–83]. Notably, whereas the auditory cortex is dispensable for the formation of fear memory, the secondary auditory cortex (Te2) has a critical role in the retrieval of fear memory long after conditioning[24, 26]. Lesions of Te2 performed 30 d, but not 24 h, after conditioning impair fear retrieva [26], and conditioning increases the expression of the neuronal activity marker *zif*268 in Te2 30 d after, but not 24 h after, learning[24, 26]. Together, these results suggest that the role played by the auditory cortex in fear conditioning is not restricted to stimulus processing and transmission, but rather, for retrieval of fearful stimuli long after associations are established[84].

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 d after conditioning depends on activity in the aCC, but not in the hippocampus[16]. Retrieval of fear memories at 24 h or 36 d time points 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 postconditioning week disrupts memory consolidation[85]. While 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.

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[27, 42, 66, 77]. A recent study demonstrated that PL is necessary for retrieval of fear at both 6 h and 7 d after conditioning, but the target of PL efferent fibers shifts across the two time points[27]. PL neurons projecting to BLA are necessary for retrieval at 6 h (but not 7 d), whereas PL neurons projecting to the paraventricular nucleus of the thalamus (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[27, 76, 86]. While 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.

Basolateral amygdala's role 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 most of the evidence coming from experiments using post-training lesion techniques. Indeed, excitotoxic lesions of BLA performed 7 days, 14 days, or 16 months after fear conditioning produced significant deficits in fear retrieval[3, 87], suggesting that BLA is an important substrate to store remote fear memories. Nevertheless, because lesion techniques provide an inaccurate control of the lesion size, it is difficult to determine whether the effects observed are due to non-specific lesion of adjacent areas (e.g. CeA, ITCs). Recent studies 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 after fear acquisition had no effect on fear retrieval tested 3 days later, suggesting that BLA is dispensable for fear memory retrieval long after conditioning[88, 89].

Further evidence that BLA activity is not required for late fear memory retrieval is our finding showing that optogenetic silencing of either BLA neurons or PL-BLA communication blocked the retrieval of 6 h-old, but not 7 d-old fear memories[27]. 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 d after conditioning[27]. Altogether, there is increasing evidence that although BLA participates in the acquisition and early retrieval of fear memory, late retrieval of fear memories may occur independent of BLA. A time-limited role of BLA neurons in memory retrieval may augment the availability of BLA neurons for new associations, with more permanent storage of emotional memories occurring in cortical structures (e.g. mPFC) where contextual and emotional information are integrated with circuits involved in decision-making[90]. While the mechanisms by which fear memories are transferred away 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.

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, IL, BLA, CeA and PAG[86, 91, 92]. A role of PVT in fear retrieval at the 24 h time point has been suggested by

previous studies using lesion or pharmacological inactivation[93, 94]. 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[28]. A parallel study combining pharmacological inactivation and optogenetic techniques in rats demonstrated that, following conditioning, PVT becomes increasingly necessary for fear memory retrieval[27]. Unlike BLA, PVT is not required for retrieval 6 h after conditioning, but is required at 24 h and thereafter. In addition to the impairment of fear retrieval, pharmacological inactivation of PVT at late time points (tested at 7 and 28 d) significantly hindered fear memory retrieval in a subsequent drug free session, suggesting that activity in PVT neurons may also be necessary for the maintenance of fear memory[27].

These recent findings argue for PVT as an important regulator of fear memories, which becomes 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[28], and a fraction of PVT neurons displays increased spontaneous firing rate within 2 h post conditioning[27]. However, transient pharmacological inactivation of the dorsal midline thalamus, including PVT, immediately prior to conditioning had no effect on fear memory retrieval assessed 24 h later[93]. In addition, chemogenetic inhibition of PVT neurons, starting from the onset of conditioning, does not affect the fear conditioning-induced synaptic plasticity onto SOM^+ CeL neurons – a recently identified cellular process critical for fear memory formation[36] – at 3 h following conditioning[28]. By contrast, the same manipulation does impair this CeL plasticity when assessed at 24 h following conditioning[28]. One possible explanation for the latter effect is that ongoing PVT activity following conditioning is required for the consolidation of CeL plasticity. Consistently, inhibiting the ongoing PVT activity with a chemogenetic approach that lasts several hours (~10 h)[95] is sufficient to impair this consolidation process[28].

Consistent with this hypothesis, the proportion of PVT neurons showing either increased tone responses or changes in spontaneous firing rate increases significantly from 2 h to 24 h post-conditioning[27]. These observations highlight PVT's importance for the maintenance, albeit not for the induction, of fear-evoked synaptic plasticity. Together with the finding that PVT becomes critical for fear memory retrieval 24 h, but not 6 h, after conditioning[27, 28], current evidence indicates that PVT regulates both the long-term expression 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 on, 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[27]. 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, which include calcium and/or voltage imaging of identified neuronal ensembles in behaving animals would help to tackle this issue[96, 97].

The PVT-amygdala circuit in fear memory regulation: While moderate projections from PVT are found in multiple amygdala nuclei, CeL is the main amygdala recipient of PVT efferent fibers[91, 92]. Rats with PVT lesions exhibit a significant increase in stress-induced cFos expression in the CeL[98]. Similarly, increased cFos expression was observed in CeL when PVT was inactivated during a fear retrieval session[93], 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[39, 59], 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[99, 100].

A closer look at the PVT-CeL microcircuit in mice reveals that PVT projections preferentially targets SOM^+ neurons of CeL, and enhance their excitability[28]. In addition, optogenetic activation of PVT afferents in CeL causes indirect inhibiton of SOM^- neurons[28], consistent with previous observations that SOM^+ CeL neurons are powerful local inhibitors[36]. 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[28].

BDNF is a critical regulator of neuronal plasticity and synaptic function[101, 102], and has been heavily implicated in memory formation[103]. In the fear circuit, BDNF regulates both fear learning in the BLA[104, 105] and fear extinction in the mPFC[106, 107]. A pivotal role of BDNF has also been reported for the persistence of fear memories[108, 109], suggesting that BDNF signaling in PVT-CeL may be a potential candidate to mediate the maintenance of fear memories. Indeed, BDNF communication between PVT and CeL neurons is critical for both fear learning and the long-term expression of fear-induced CeL synaptic plasticity[28]. In addition, because BDNF mediates PVT-CeL neurotransmission, BDNF may subserve PVT's function in fear memory maintenance, although direct evidence for this is lacking.

As previously mentioned, inactivation of PVT inputs to the CeA during a 7d fear memory retrieval session impairs the subsequent retrieval of fear memory one day later[27]. 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 MAP kinase[27], a critical mediator of neuronal plasticity[110]. 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[111]. Activation of MAP kinase signaling in PVT may strengthen the formation of fear memories, leading to impaired retrieval of extinction memories during adolescence.

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[86, 91, 92]. Our understanding of the functional role of PVT is mainly based on lesion studies, which characterize PVT as part of the brain circuitry controlling both arousal mediated by negative states and adaptive responses to stress (for review see:[112, 113]). Studies in rodents have shown that PVT is activated by a variety of physical and psychological stressors including restraint[114, 115], foot shock[116], sleep deprivation[117], and forced swim[118, 119]. In turn, PVT activity has been shown to modulate neuroendocrine[120, 121], autonomic[114, 122] and behavioral responses to stress[123]. 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 responses such as increased vulnerability to stress, exacerbated anxiety phenotypes and depressive-like behaviors such as despair, anhedonia and lack of motivation[112, 124]. Notably, pharmacological activation of PVT produces anxiety and fear-like behavior in rats[125, 126], and increased activity in PVT neurons projecting to the CeA is correlated with depressive-like behavior in rats[119], 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[127], suggesting that malfunctioning in this thalamic subregion may be also 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 in humans[128]. However, whether a link exists between PVT dysfunction and the co-expression of these pathological phenotypes has yet to be determined. Consistent with the idea of coordinating both positive and negative emotional states, PVT is activated by cues associated with either food[129, 130] or drug reward[131–133], as well as by cues associated with aversive taste[134] or fearful stimuli[27, 134, 135]. Therefore, encoding of negative valence could occur via activation of PVT projections to CeA (as discussed above), whereas encoding of positive valence could occur through activation of PVT projections to the nucleus accumbens, as previously suggested[136, 137].

In addition to its documented role in both defensive and reward-seeking behaviors, PVT has also been implicated in the modulation of circadian rhythms and energy balance in rats[114]. Notably, PVT displays diurnal variations in neuronal activity[122], and lesions of PVT abolish light-induced phase shifts in circadian rhythmicity[138]. Together, these findings depict a potential role for PVT as an important regulator of homeostasis and state-dependent behavior. Therefore, unlike BLA, PVT may be well positioned to integrate defensive

behaviors elicited by aversive memories with adaptive biological responses, which include arousal, stress-adaptation, regulation of circadian rhythms, and control of food intake and energy balance (see Fig 2).

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. 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 level - how aversive memories are retrieved across time. Prior studies of retrieval circuits have uniquely focused at the 24 hours post-conditioning time point, therefore ignoring temporal changes that occur later after the acquisition phase. Understanding how fear retrieval circuits are restructured over time may be of relevance for the treatment of post-traumatic stress disorder (PTSD), given that PTSD patients seek medical assistance weeks or even months after the initial trauma[139].

The advance of optogenetic tools, combined with calcium imaging and single-unit recording of identified neurons, have provided a unique opportunity to understand the temporal dynamic of memory reorganization. By manipulating and recording the activity of defined neural ensembles during behavior, future studies will identify time-dependent changes in the neural circuits mediating long-term retrieval of aversive memories. In addition, imaging studies focusing on the temporal modifications of retrieval circuits in humans may help to elucidate how aversive memories persist over time, thereby providing alternative targets for pharmacological treatment in patients with anxiety disorders.

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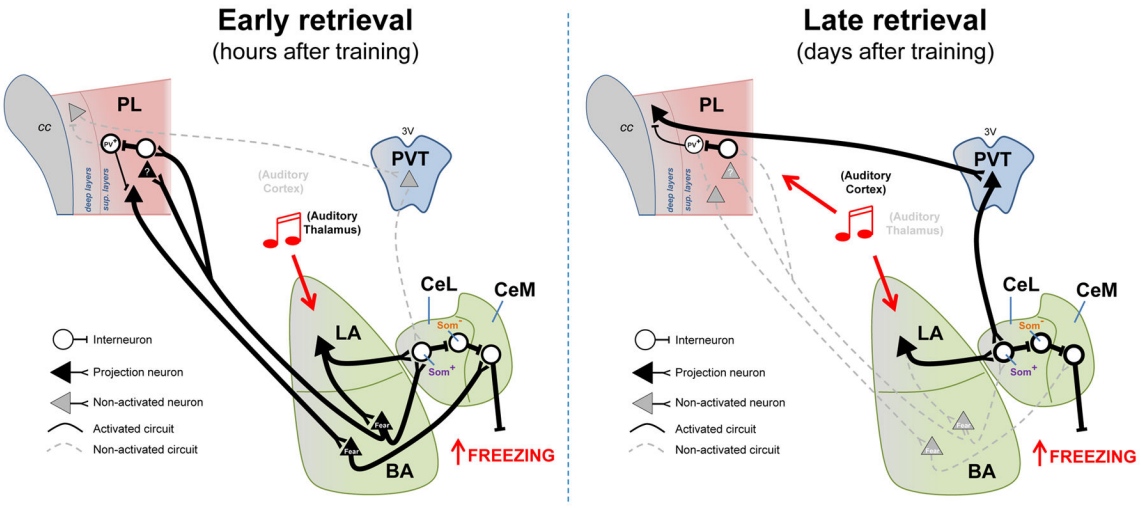

Fig. 1. Temporal reorganization of the circuits necessary for retrieval of auditory fear memories

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. *Legend:* PL= prelimbic cortex, sup= superficial, PVT= paraventricular nucleus of the thalamus, LA= lateral amygdala, BA= basal amygdala, CeL= lateral portion of the central amygdala, CeM= medial portion of the central amygdala, cc= corpus callosum, 3V= third ventricle, PV^+= parvalbumin positive neurons, Som^+= somastotatin positive neurons, Som^-= somatostatin negative neurons.

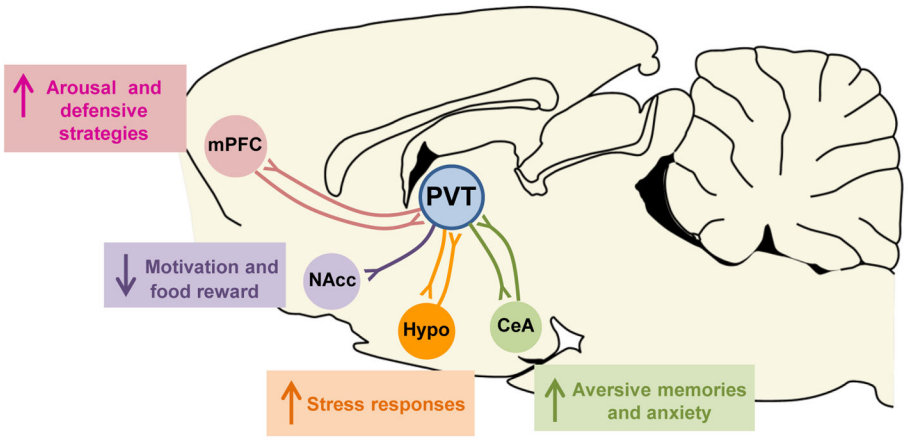

Fig. 2. Recruitment of PVT into the fear circuit may serve to integrate aversive memories with adaptive biological responses

The paraventricular nucleus of the thalamus (PVT) is reciprocally interconnected with the medial prefrontal cortex (mPFC), the hypothalamus (Hypo), and the central nucleus of the amygdala (CeA). In addition, PVT is the major source of inputs to the nucleus accumbens (NAcc). This pattern of anatomical connections places PVT in a central position to integrate aversive memories and anxiety (through connections with CeA) with adaptive biological responses such as arousal and defensive strategies (through connections with the mPFC), motivation and control of food intake (through projections to the NAcc), and regulation of circadian rhythms and stress responses (through connections with the hypothalamus).