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Threat Memory in the Sensory Cortex: Insights from Olfaction

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Abstract

The amygdala has long held the center seat in the neural basis of threat conditioning. However, a rapidly growing literature has elucidated extra-amygdala circuits in this process, highlighting the sensory cortex for its critical role in the mnemonic aspect of the process. While this literature is largely focused on the auditory system, substantial human and rodent findings on the olfactory system have emerged. The unique nature of the olfactory neuroanatomy and its intimate association with emotion compels a review of this recent literature to illuminate its special contribution to threat memory. Here, integrating recent evidence in humans and animal models, we posit that the olfactory (piriform) cortex is a primary and necessary component of the distributed threat memory network, supporting mnemonic ensemble coding of acquired threat. We further highlight the basic circuit architecture of the piriform cortex characterized by distributed, auto-associative connections, which is prime for highly efficient content-addressable memory computing to support threat memory. Given the primordial role of the piriform cortex in cortical evolution and its simple, well-defined circuits, we propose that olfaction can be a model system for understanding (transmodal) sensory cortical mechanisms underlying threat memory.

Keywords

distributed memory, engram, fear, olfactory conditioning, pattern recognition, sensory encoding, sensory mechanisms, threat encoding

Introduction

One of the most influential tenets in affective neuroscience is that the amygdala complex plays a central role in threat processing (with the subjective feeling "fear" involving other higher-order circuits; LeDoux 2022). However, while support for this idea is overwhelming, dissents have been opined from time to time (Paré 2002; Weinberger 2004). Lately, meta- and mega-analyses of human amygdala responses to threat conditioning (see Glossary) have questioned the extent of its role in humans (Fullana and others 2016; Fullana and others 2018; Visser and others 2021; but also see Wen and others 2022). It is thus still debatable whether evidence of amygdala's *essential* role reflects its *sufficient*, *central* role in all aspects of threat processing and across humans and mammalian animal models. At the heart of this debate stands the controversy of whether the amygdala is the root of threat memory (i.e., the locus of threat engram; see Glossary).

Interestingly, from early on, pioneers of amygdala research have asserted a view of a distributed, complex network of threat memory (Fanselow and LeDoux 1999). In fact, at the conclusion of the high-profile end-of-the-century debate (Fanselow and LeDoux [1999] vs. Cahill and others [1999], published back-to-back), the amygdala camp (Fanselow and LeDoux 1999) had recognized the possibility that cortical areas participate in threat memory: "It seems possible that the ABL [amygdala-basolateral], while essential, is also part of a distributed network that encodes the fear memory. . . . Cortical areas that are both afferent and efferent to the ABL (e.g., perirhinal cortex, the hippocampal formation, and sensory cortex) may participate with the ABL in the long-term encoding of fear." However, in the ensuing decades of the new millennium, research into the amygdala has exploded and pushed the amygdala to the center of not

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only threat conditioning but threat processing in general. By contrast, other regions have receded to the periphery.

In fact, a large body of evidence implicating extra-amygdala substrates of threat conditioning (in the sensory cortex and hippocampus) had existed long before the amygdala ascended into the limelight (Cahill and others 1999; Galambos and others 1955). In the past decade, this literature, particularly concerning the sensory cortex, has experienced a resurgence powered by the rapid advancement in technology. As described below, evidence for a role of the sensory cortex in threat conditioning (especially long-term threat memory) in both humans and animal models is growing. While the auditory cortex is the most studied in this literature, substantial evidence from the olfactory cortex has also accrued. The olfactory cortex has a simple and well-studied circuit architecture, which epitomizes a content-addressable memory (CAM; see Glossary) computing system known for highly efficient memory storage and retrieval. Therefore, the olfactory cortex may provide particularly useful insights as a model system for the study of threat memory.

Sensory Cortex and the Threat Engram

Threat Conditioning Generates Associative Plasticity in the Sensory Cortex

The sensory cortex builds its own record of threat conditioning by revising neuronal ensemble coding of the conditioned stimulus (CS) via a distinct set of plastic changes, including altered neuronal excitation/inhibition balance, receptive field sharpening/expansion, tuning shifts, and pattern separation (Fig. 1A). Such associative plasticity has been observed in all sensory cortices in a CS modality-specific manner. The plasticity in the sensory cortex shows a strong time dependence. While emerging within a few trials, associative plasticity in the sensory cortex persists (in contrast to amygdala changes known to reset after several trials; Fanselow and LeDoux 1999) and, moreover, becomes stronger and more stable over time (Li 2014; Weinberger 2004; Wilson and Sullivan 2011) (Fig. 1B).

Threat Conditioning Involves Bidirectional Sensory-Cortex-Amygdala Interaction

This sensory cortical plasticity is associated with strong bidirectional interaction between the sensory cortex and the basolateral amygdala. The amygdala can project to the sensory cortex to promote sensory cortical plasticity (Armony and others 1998). Importantly, this amygdala projection strengthens over days to support the development of threat memory (Yang and others 2016). Conversely, threat conditioning induces cortical input synaptic plasticity (i.e., long-term potentiation of sensory cortical synaptic projections to the amygdala), and selective inhibition of this synaptic plasticity impairs long-term threat memory (Fourcaudot and others 2009; Huang and Kandel 1998). Recent evidence has further emphasized that this sensory cortical input to the amygdala plays a key role in the formation and storage of threat memory (Cambiaghi and others 2016; Dalmay and others 2019; East and others 2021). These findings thus confirm the common origin of associative plasticity in the basolateral amygdala and sensory cortex and emphasize their interactive participation in threat memory.

Sensory Cortex Is Essential for Long-Term Threat Memory

The sensory cortical participation is highly time dependent. Early work demonstrated that lesions in the amygdala but not the sensory pathway (including the sensory midbrain, thalamus, and cortex) impaired threat conditioning (Fanselow and LeDoux 1999). These findings were very influential in establishing the essential role of the amygdala (over the sensory cortex). However, early lesion studies in the sensory cortex examined primarily the early phase of threat conditioning (i.e., conditioning acquisition and consolidation but not long-term memory, e.g., $>$24 hours or days). More recently, a large study in rodents studied long-term, remote memory and demonstrated that lesions in the (secondary) sensory cortex across auditory, visual, and olfactory modalities impaired expression of threat conditioning acquired one month earlier while leaving conditioning acquisition and consolidation intact (Sacco and Sacchetti 2010). Subsequent work from the Sacchetti group and others has corroborated these findings using both lesion and experimental manipulations (see Concina and others [2019] for an excellent review on the auditory cortex). This necessary role of sensory cortical plasticity in long-term threat memory, combined with its time-dependent plasticity, highlights the sensory cortex as a crucial locus of the permanent repository of threat conditioning (Concina and others 2019; Weinberger 2004).

Threat Memory Is Stored in a Distributed Network

The research has thus established a system of threat conditioning in the sensory cortex, in parallel to the amygdala. Very recently, a network conceptualization of threat conditioning has gained traction. Specifically, threat memory is represented by a constellation of representations (i.e., individual engram components) stored in a distributed network, including the amygdala, sensory cortex,

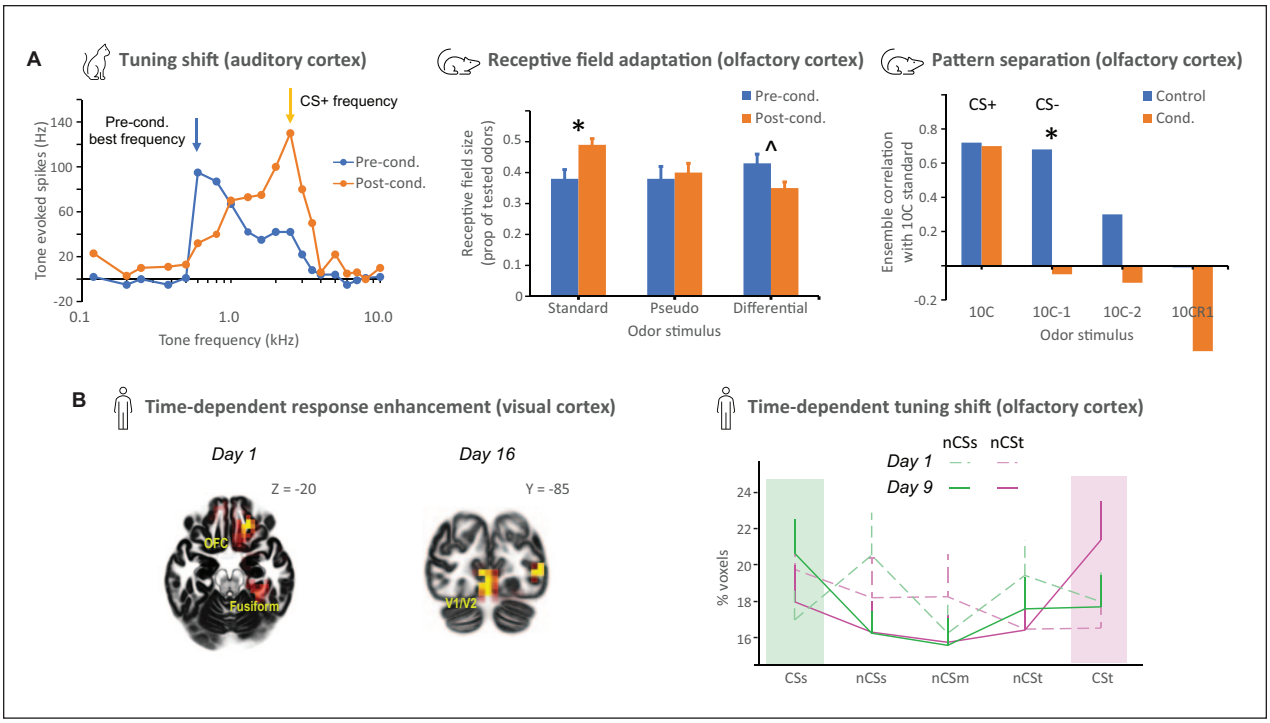

Figure 1. Associative plasticity via conditioning in the sensory cortex across modalities and species. (A) Examples of associative plasticity in the sensory cortex induced by conditioning (Cond.). Left: Tuning shift. In this example of associative plasticity in the cat auditory cortex, following association of a tone conditioned stimulus (CS) with shock, the frequency most effective at driving the cell (best frequency) before conditioning shifted toward the CS+ frequency. Adapted from Weinberger (2004). Middle: Receptive field adaptation. Following *standard* olfactory threat conditioning (a CS+ odor paired with shock), animals (rats) showed generalized freezing responses to many odors. This generalized fear response (to non-CS) was associated with a broadening of olfactory (piriform) cortex single-unit response receptive fields (e.g., reduced acuity). In contrast, following *differential* conditioning using both a CS+ and a CS–, rats showed CS-specific freezing and a concomitant narrowing of piriform cortex receptive fields (e.g., increased acuity). Adapted from Chen and others (2011). Right: Pattern separation. This example illustrates similar associative plasticity in rodent piriform cortex following appetitive conditioning. Animals were required to discriminate overlapping 10 component (10C) odor mixtures (e.g., with 10C as the standard and other mixtures missing one or two components or having one component replaced [10CR1]). In rats trained to discriminate 10C from 10C-1, piriform cortical ensembles became much better at decorrelating those odors, compared to rats training on a much simpler discrimination. Adapted from Chapuis and Wilson (2012). (B) Time-dependent associative plasticity in the sensory cortex. Left: Among human subjects who underwent differential visual threat conditioning, associative plasticity (enhanced response to CS+ vs. CS–) emerged in a distributed network immediately after conditioning (day 1) and shifted to the early visual cortex (V1/V2) at the retention test on day 16, accompanied by plasticity strengthening (even greater response to CS+ vs. CS–). Adapted from You and others (2021). Right: Among human subjects who underwent differential olfactory threat conditioning (involving CS-threat/CSt and CS-safety/CSs), over 20% of olfactory piriform voxels that were identified as tuned (maximally responsive) to the non-CS (nCSt and nCSs) before conditioning became tuned to the similar CS+ (CSt and CSs, respectively), albeit only on day 9 (but not on day 1). Adapted from You and others (2022).

hippocampus, insula, and the prefrontal cortex, each substantiating a specialized aspect of threat memory (Headley and others 2019; Josselyn and Tonegawa 2020). It stands to reason that in this network, the sensory cortex stores the sensory aspect of threat memory (i.e., the sensory threat engram) via modified neuronal ensemble coding of CS sensory input (as exemplified in Fig. 1).

Empirical, computational, and theoretic neuroscience models of memory have converged on the idea that engrams exist as distributed, auto-associative ensembles of neurons formed and shaped through associative experiences (Gerstner and others 2012; Josselyn and Tonegawa 2020). Accordingly, the mystery of engrams would lie in the associative circuitry of such neuronal ensembles. The participation of the olfactory cortex (primarily, the piriform cortex) in olfactory threat conditioning has been clearly evinced. Moreover, the circuitry of the piriform cortex has been well defined and, importantly, has been likened to a CAM system and thus a good model for studying memory engrams (Haberly and Bower 1989).

Therefore, research into the olfactory cortex would hold promise for understanding the sensory threat engram specifically and the entire threat engram in general.

Olfactory Cortex—A Model System for Study of the Sensory Threat Engram

Threat Engram in the Olfactory Cortex

There is abundant evidence from rodents to humans to support associative plasticity in the piriform cortex following olfactory threat conditioning (Chen and others 2011; Li 2014; Wilson and Sullivan 2011). Similar to other sensory modalities, associative plasticity in the piriform cortex takes the form of ensemble pattern modification, tuning shifts, receptive field adaptation, and changes in cortical oscillations putatively due to changes in neuronal excitation/inhibition balance (Barnes and others 2011; Chapuis and Wilson 2012; Chen and others 2011; Li and others 2008; Motanis and others 2014; You and others 2022) (Fig. 1A). The involvement of bidirectional amygdala-piriform interaction is also supported by findings of enhanced connectivity and bidirectional information flow between the amygdala and piriform cortex following threat conditioning and aversive experience (East and others 2021; Krusemark and others 2013).

The necessary role of the piriform cortex is evinced by the fact that lesions of the piriform cortex (without impairing basic olfactory processing) can block the expression of threat conditioning tested a day (East and others 2021) or a month later (Sacco and Sacchetti 2010), and blockade of NMDA receptors in the piriform cortex can impair long-term (but not recent) memory of threat conditioning (Hegoburu and others 2014). In addition, chemogenetic silencing or reactivation of piriform neuron ensembles active during olfactory threat conditioning can impair or evoke threat memory, respectively, causally elucidating this piriform engram (Choi and others 2011; Meissner-Bernard and others 2019).

Moreover, this plasticity also exhibits time-dependent properties, more prominent in long-term threat memory (Hegoburu and others 2014; Mouly and others 2022; You and others 2022) (Fig. 1B). Notably, applying neuroimaging methods (fMRI and PET) for large-scale, whole-brain analysis combined with temporal profiling of associative plasticity over a long delay, two new studies (in rodents and humans) demonstrated that the piriform cortex exhibits associative plasticity both soon and long after threat conditioning, in contrast to transitory (or no) plasticity in the amygdala and frontal cortices (Mouly and others 2022; You and others 2022). These effects are consistent with findings from human fMRI and electrophysiologic studies in the visual and auditory cortices, which indicated lasting associative plasticity in the sensory cortex in contrast to transitory plasticity in the amygdala and inferotemporal and orbitofrontal cortices (Apergis-Schoute and others 2014; You and others 2021). Interestingly, in a manner that can be likened to the hippocampus, the piriform cortex in rodents shows sleep-dependent memory replay that is important for accurate threat memory consolidation (Barnes and Wilson 2014), further emphasizing the long-term nature of olfactory cortical memory engrams.

Olfactory Cortex Holds Basic Circuit Architecture for Threat Memory

The olfactory piriform cortex is evolutionarily the oldest laminated cortex, emerging in the ancestral amniote brain and long predating the advent of amygdala. That threat conditioning is widely observed in amniotes (e.g., reptiles) implies that this ancient cortex is not only necessary but largely sufficient for threat conditioning (at least, in simple forms). Notably, the basic structure of the piriform cortex is highly conserved through evolution and shows minimal differences across mammals (including humans), in fitting with the convergence of results in threat memory studies across species. The proficiency of the piriform cortex in threat memory is likely to arise from its combination of local circuit architecture and its privileged connectivity within the broader threat network (as reviewed below).

Circuit architecture optimal for CAM of threat engram. The piriform cortex is characterized by a three-layered cortical circuit organization comprising basic circuit units each centered on a pyramidal neuron receiving auto- and inter-associative feedforward and feedback excitation and inhibition; moreover, these circuit units are widely distributed throughout layers II and III of piriform cortex (Shepherd and Rowe 2017) (Fig. 2). As noted above, this circuit architecture is characteristic of a CAM processor, enabling highly efficient memory storage and retrieval, particularly for associative memory (Haberly and Bower 1989). Through this circuit architecture, olfactory pyramidal neurons would form distributed, combinatorial ensembles supporting the threat engram associated with the CS odor (Fig. 2B). Importantly, this engram is adaptable as the neuronal ensemble pattern is modified by adding or deleting constituent circuit units and strengthening and weakening synaptic connectivity between the circuit units. In addition, this engram is efficient given that the CAM processor permits incomplete or degraded odor information (received within a single sniff) to activate the entire neuronal ensemble (Pashkovski and others 2020; Wilson and Sullivan 2011) (Fig. 2B). As such, the CAM architecture in the piriform cortex ensures strong ecological advantage

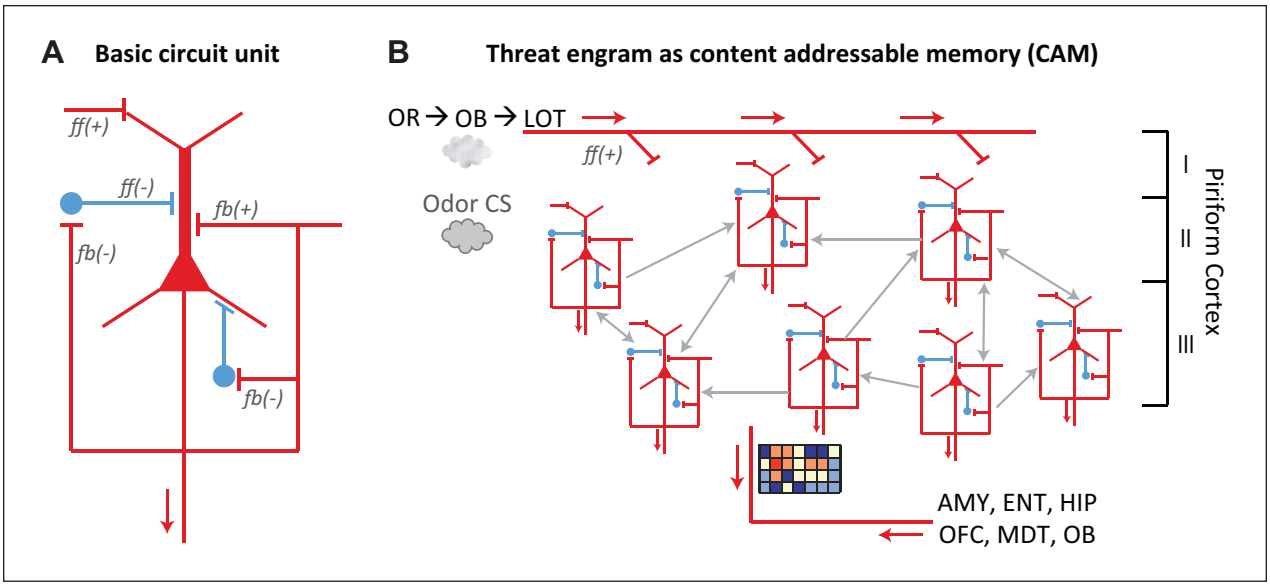

Figure 2. Schematic circuit architecture of the piriform cortex optimal for content-addressable memory (CAM). (A) Well-defined basic circuit unit in the piriform cortex, characterized by autoassociative feedforward (ff) and feedback (fb) excitation (+) and inhibition (–). Adapted from Shepherd and Rowe (2017). (B) These basic circuit units are widely distributed in layers II to III and receive excitatory input from the olfactory bulb (OB) that synapses in layer I. Together, they form a densely connected network to support ensemble neural representations that are capable of CAM (a highly efficient form of memory). As such, incomplete or degraded conditioned stimulus (CS) odor information (received even within a single sniff) at the olfactory receptor (OR) can activate the entire threat memory and support accurate, complete representation of the odor in the piriform cortex, which then activates a distributed network for downstream threat processing. Primary areas include the amygdala (AMY), entorhinal cortex (ENT), hippocampus (HIP), orbitofrontal cortex (OFC), medial dorsal thalamus (MDT), and olfactory tubercle (OT), as well as back projections to the OB and association connections within the piriform cortex. LOT, lateral olfactory tract.

of the threat engram: it adapts quickly with the environment and context and performs accurate pattern recognition for a fleeting threat odor at a high speed.

Strategic location of piriform cortex in the threat network. The piriform cortex is further characterized by strong associations with key structures in the threat network. In both rodents and primates, including humans, the anatomic network and functional (intrinsic as well as odor-evoked) network of olfaction both map closely onto the threat network (Arnold and others 2020) (Fig. 3). In the mammalian brain, the piriform cortex can be divided into anterior and posterior regions based on circuit structure, with the anterior dominated by input from the olfactory bulb and the posterior being much more associative and receiving extensive input from diverse nonolfactory regions (Wilson and Sullivan 2011). Specifically, the (posterior) piriform neurons are connected with a wide web of telencephalic structures, including the amygdala, entorhinal cortex, insula, and prefrontal cortex, strongly implicated in the threat engram (Josselyn and Tonegawa 2020; Shepherd and Rowe 2017). The bidirectional connection between the piriform cortex and multiple amygdala nuclei is far more robust than that described for other sensory systems (Aggleton and Saunders 2000), with exception of the insular cortex and taste (Fontanini and Katz 2009), suggesting relatively privileged access to threat processing in the chemical senses relative to other sensory cortices. Furthermore, multisensory convergence occurs in the piriform, especially posterior piriform, allowing formation of association between the CS and unconditioned stimulus (US) in situ (Sadrian and Wilson 2015) and potentially even with spatial context to support threat contextualization (Poo and others 2022). Therefore, evolution appears to have strategically positioned the (posterior) piriform cortex in the connectome such that it can integrate the sensory threat engram with the distributed network of the threat engram.

Olfactory Threat Engram—The Source Code for Neocortical Sensory Threat Engram

As the primordial cortical structure, the piriform cortex contains the primary motif of cortical circuits, which was extended to the dorsal cortex (later evolving into the neocortex) and hippocampus (Shepherd and Rowe 2017). Therefore, the powerful circuit architecture of the piriform cortex could have been co-opted in the formation of

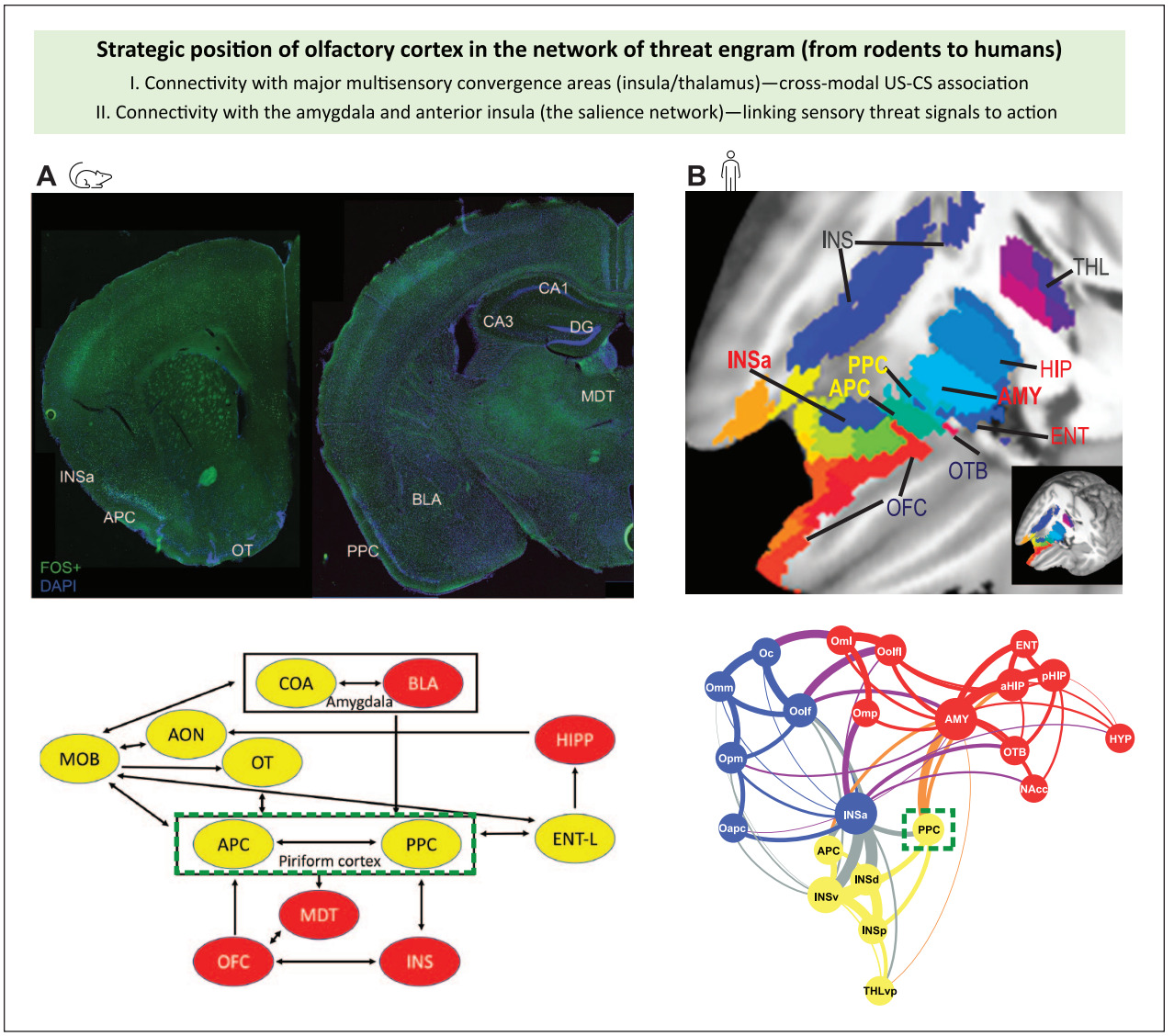

Figure 3. Strategic position of the piriform cortex in the threat network. (A) Close correspondence of olfactory and threat networks in rodents. Top: Coronal sections through regions of the rodent olfactory network involved in odor threat memory. FOS+ labeling is shown in response to simple odor enrichment exposure to emphasize breadth of circuit activation. Regions labeled include the anterior piriform cortex (APC), agranular insula cortex (INSa), olfactory tubercle (OT), posterior piriform cortex (PPC), basolateral amygdala (BLA), dorsal medial nucleus of the thalamus (MDT), and hippocampal regions CA1, CA3, and dentate gyrus (DG). Bottom: Schematic diagram of extended olfactory system (yellow) including monosynaptic partners (red) that may be involved in associative memory and coding of hedonic valence within the piriform cortex. PPC occupies a central location in the network. AON, accessary olfactory nucleus; BLA, basolateral amygdala; COA, cortical nucleus of amygdala; ENT-L, entorhinal cortex-lateral; HIPP, hippocampus; MOB, main olfactory bulb; OFC, orbitofrontal cortex. (B) Close correspondence of olfactory and threat networks in humans. Top: Three-dimensional (3D) display of key regions in the *anatomic* olfactory network, homologous to the rodent system as shown in panel A (bottom). The olfactory PPC is centrally positioned in the network. The inset illustrates 3D whole-brain image with parts of the dorsolateral frontal and temporal lobes removed. Bottom: Topology of the *functional* olfactory network (extracted from ~800 human subjects) indicates the central location and connector (cross-module) hub function of the PPC. Graph-theoretical analysis identified three modules/subnetworks—olfactory (yellow), limbic (red), and OFC (blue). Line thickness indicates connection strength, and node size reflects connection density (number of connections). INSa/p/v/d, anterior, posterior, ventral, and dorsal segments of the insula; NAcc, nucleus accumbens; OTB, olfactory tubercle; Oxx, different parcels of the OFC; THL, thalamus; THLvp, ventral posterior segment of the thalamus. Adapted from Arnold and others (2020).

the neocortical sensory cortices. The six layers in the neocortex are considered the duplicated three-layer piriform cortex with its primary neurons occupying all layers from layers II to VI and the neocortical innovations—pyramidal tract (PT) and corticothalamic (CT) neurons—confined to layers V/VI (Shepherd and Rowe 2017). Importantly, associative plasticity related to long-term memory of threat conditioning (e.g., protein synthesis) largely appears in layers II to IV of the neocortex (Gdalyahu and others 2012; Sacco and Sacchetti 2010). Therefore, the basic circuit in the piriform cortex appears to dominate in the neocortical sensory cortex, particularly the circuitry for threat memory. As such, the CAM architecture and adaptive autoassociative ensemble threat representation in the piriform cortex may have been universally adopted across modalities. In this sense, the ancient olfactory cortex may hold the source code for the sensory threat engram in general, while properties of individual (e.g., auditory, visual) sensory cortices and their connectivity within the threat network would complete their respective engrams with modality-specific characteristics.

Conclusion

Threat conditioning remains an important problem in affective neuroscience. Pendulum swings and controversies notwithstanding, intense research on this topic has brought the field to a distributed view of threat memory. In this distributed network, the amygdala is indeed essential, but so is the sensory cortex (and potentially other structures), albeit in distinct ways. Establishing the sensory cortical representation of threat memory would have important implications in the conceptualization of threat processing and fear-related disorders. In confronting danger in the environment, an organism needs to maintain an accurate memory of acquired signals of threat. The sensory cortex is on the frontline, enacting threat evaluation in the initial sensory feedforward sweep and subsequently alerting and triggering the other systems into action. Abnormal functioning of sensory threat memory (e.g., hyperfunctioning, decontextualization) could underlie the pathophysiology of fear-related disorders (such as posttraumatic stress disorder), accounting for the extreme fear of trauma-related sensory cues and intrusive memories laden with vivid sensory fragments of the traumatic event (Brewin and others 2010; Li 2019). As such, unlocking the sensory threat engram would enable the modification and erasure of threat memory, revolutionizing clinical intervention of such disorders. The olfactory cortex, equipped with a simple and well-understood CAM circuit architecture, would serve as a particularly useful model system.

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Glossary

Content-addressable memory (CAM): A highly efficient form of memory that allows distributed information storage through convergent activity of feedforward inputs, which can facilitate associative memory of diverse inputs (e.g., olfactory, multisensory context, and hedonic state) and then be recalled by just a subset of those original inputs.

Threat conditioning: A highly reliable experimental paradigm that renders an initially neutral cue (i.e., conditioned stimulus/CS) threatening by associating it with an aversive unconditioned stimulus (US).

Threat engram: Necessary and sufficient neural changes encoding the learned threat.

Declaration of Conflicting Interests

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