Trends in Cognitive Sciences

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Opinion

Sensing fear: fast and precise threat evaluation in human sensory cortex

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Animal models of threat processing have evolved beyond the amygdala to incorporate a distributed neural network. In human research, evidence has intensified in recent years to challenge the canonical threat circuitry centered on the amygdala, urging revision of threat conceptualization. A strong surge of research into threat processing in the sensory cortex in the past decade has generated particularly useful insights to inform the reconceptualization. Here, synthesizing findings from both animal and human research, we highlight sensitive, specific, and adaptable threat representations in the sensory cortex, arising from experience-based sculpting of sensory coding networks. We thus propose that the human sensory cortex can drive smart (fast and precise) threat evaluation, producing threat-imbued sensory afferents to elicit network-wide threat responses.

Highlights

Human sensory cortex is equipped with a highly associative architecture capable of complex functions beyond feature analysis.

Human sensory cortex independently performs both fast and precise threat processing.

Sensory cortical plasticity develops from aversive experiences (e.g., threat conditioning), and over time, evolves into long-term memory traces stored as mnemonic representations of threat cues.

Sensory threat representations enjoy high sensitivity, specificity, and adaptability through experience-based sculpting of sensory coding networks (via ensemble pattern modification, tuning shift, disinhibition, and sparsification).

A sensory account is proposed to highlight smart initial threat evaluation in the human sensory cortex, evoking multifaceted threat processing across a distributed neural network, orchestrated to drive rich, flexible threat responses in humans.

Threat processing: looking beyond the amygdala

The neural basis of threat processing (e.g., threat evaluation, detection, and identification as well as defensive responses) is an important and enduring topic in cognitive neuroscience. By the end of the past century, the amygdala had catapulted onto the center stage of theories of threat processing, through a series of seminal studies and influential reviews [1–3]. The enormous success of this pioneering work has led to large swaths of basic, translational, and clinical research targeting the amygdala in threat processing and fear-related disorders. In this research, especially in humans, amygdala involvement is taken as both a premise and a benchmark of threat processing.

Such overwhelming anointing of the amygdala may have astonished early pioneers, who cautioned that 'the amygdala is not the brain's fear center' [4,5]. In fact, evidence incompatible with the amygdala-centric view continues to arise, prompting dissenting perspectives that emphasize a distributed network view involving multiple waves and pathways across the cortex and subcortex for threat processing [6,7]. Strikingly, in humans, several new meta- and mega-analyses of neuroimaging studies of threat conditioning failed to identify the involvement of amygdala, questioning its dominance in human threat processing [8–10]. While absence of evidence is not evidence of absence, and weak but reliable effects in the human amygdala likely exist [11], there is an urgent need to look beyond the amygdala for the neural basis of threat processing.

As early as the 1950s, the basic (primary and secondary) sensory cortex was found to participate in threat conditioning in animals [12,13]. Drawing on rapid advances in technology, a recent surge of animal research into the sensory cortex in threat conditioning has expanded its critical role in threat processing [14,15]. In human threat research, however, the basic sensory cortex has been largely overlooked. Nonetheless, a substantial body of evidence has accrued to suggest that the human sensory cortex also plays an active role in threat processing. This article reviews the extant evidence and proposes a sensory cortical account of threat processing: the sensory cortex stores mnemonic representations of threat that are sensitive, specific, and adaptable,

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driving smart (fast and precise) initial evaluation of environmental threat and eliciting cascades of network-wide threat responses.

Threat evaluation in human sensory cortex

More than a sensory analyst

It is generally accepted (or may even be 'unanimously assumed' [16]) that the sensory cortex is absent from initial threat evaluation, faithfully encoding physical (but not abstract; e.g., emotional) features of environmental cues. While it is recognized that rudimentary processing of innate threat cues may be achieved in lower-order sensory areas (e.g., sensory thalamus and peripheral sensory receptors) [16,17], to date, threat theories have largely focused on a selective, encapsulated amygdala-centric circuit [18], which detects threat in environmental input and projects instructive signals to the sensory cortex to enable threat perception [19]. Accordingly, sensory cortices are thought to participate in threat processing passively, subservient to top-down instruction from structures such as the amygdala.

The encapsulated threat circuit is considered an evolutionarily conserved system traceable to the ancient amniotic (reptilian) brain [20]. Ironically, the olfactory sensory cortex (i.e., piriform cortex), the first laminated cortex in the brain, had emerged in the ancestral amniote long before the advent of amygdala (or its more ancient limbic partner – the hippocampus) [21,22]. In addition, selective, flexible threat responses (e.g., threat conditioning) are widely observed throughout the phylogeny [23]. This suggests that the olfactory sensory cortex was able to perform both sensory and threat processing. In fact, the basic architecture of the piriform cortex is characterized by **microcircuit networks** (see Glossary) of auto- and interassociative feedforward and feedback excitatory and inhibitory projections [21,22]. Such an architecture is poised to support distributed, combinatorial analysis and higher-level, associative functions including complex threat processing [24,25].

Evolution has preserved this efficient machinery. The piriform cortex is highly conserved across species; its basic architecture is virtually identical across mammalian brains [21,22], suggesting that its ancient function of complex threat processing is also conserved in humans. Furthermore, converging histological, physiological, and connectional evidence suggests that the piriform architecture was co-opted in the evolution of the neocortex, including the sensory cortex of the later senses (vision, audition, and somatosensation): the three layers of the piriform cortex (along with its microcircuit architecture) essentially duplicated (by evolving sublayers) to form the six-layer neocortex [21,25]. As such, complex functions built into the piriform cortex were inherited by the neocortex. The piriform primary neurons, known as intratelencephalic neurons, are densely connected with telencephalic structures, including key regions for threat processing such as the amygdala and hippocampus. With this foundation, two key neocortical innovations, pyramidal tract neurons and corticothalamic neurons, further transmit neocortical input to the brainstem and thalamus, promoting sensory cortical regulation of subcortical threat processing and responses. Therefore, the neocortical sensory cortex is likely purposed for even more sophisticated (yet underappreciated) functions, especially for threat stimuli [26].

Threat encoding in human sensory cortex

Initial attempts to locate threat encoding in the human sensory cortex using fMRI (including fMRI multivoxel pattern analysis) were carried out by two independent groups almost simultaneously. By applying olfactory and visual threat conditioning, they demonstrated divergent activation patterns in the olfactory piriform cortex and enhanced responses in the visual (V1) cortex for the conditioned stimuli (CSs) versus unconditioned stimuli, respectively [27,28]. The past decade has seen a rapid expansion of this literature. fMRI studies of threat conditioning not only corroborated earlier findings in the visual and olfactory cortex [29–31] but also extended them to the basic

Glossary

Acquired associative representation (AAR): response and connectivity properties of sensory cortical neurons readily change through associative experience (e.g., conditioning), altering the microcircuit network of sensory coding. This network alteration results in a new sensory code (an AAR) to represent the acquired sensory object (e.g., threat CS) that is defined by both its (invariant) sensory features and acquired association.

Cortical map expansion: enlargement of extent of cortical neurons responsive to a stimulus, especially those of high biological salience and ecological relevance. Expansion is often at the cost of cortical representation areas associated with less relevant, or less used, stimuli or behaviors.

Microcircuit networks: microcircuits linking primary neurons and interneurons across the cortical layers are interdigitated to form microscopic networks. The neuronal composition and connectivity pattern for such a network are moderately stereotyped and together encode a specific stimulus or behavior.

Neuronal ensemble: group of interconnected neurons that tend to be coactivated to encode a specific stimulus or behavior.

Pattern separation: process in which the spatial or temporal activation patterns of (often similar) neuronal ensembles become more distinct.

Response tuning: differential or selective neuronal responses along a feature dimension, such as contrast, pitch, or orientation. The response change over a feature gradient is characterized as the tuning function or tuning curve. Examples for tuning functions include the varying response of auditory neurons to different pitches (frequencies), or of visual neurons to different spatial orientations of a grating or line.

Sparse coding/sparsification: notion that a recurring, predictable stimulus or behavior may have progressively reduced neuronal firing rates and/or number of responsive neurons. Sparse coding networks are thought to have lower energy expenditure as well as rapid activation and high selectivity to the encoded stimulus or behavior.

auditory cortex [32–34]. fMRI research has also demonstrated encoding of threat from complex real-world scenes in the basic sensory cortex [35,36]. Importantly, that such processing can be preserved in patients with amygdala lesions [35] suggests its independence of instructive signals from the amygdala (in contrast to the standard view).

Further evidence can be drawn from a long-standing literature on human electrophysiology of threat processing. Due to its proximity to the scalp, the sensory (visual, auditory, and somatosensory) cortex is highly accessible for human electroencephalography (EEG). In addition, the high temporal resolution of EEG, assisted by intracortical source estimation based on high-density recordings, has permitted the identification of threat processing in the early sensory cortex and helped dissociate it from amygdala-based threat processing (Figure 1A–C). In this literature, rapid threat responses (for simple cues or complex scenes) have been repeatedly observed in the sensory cortex at latencies of 50–120 ms [16,37–40]. The fast responses to simple threat cues (e.g., gratings associated with conditioned threat; 50–70 ms) (Figure 1B) have been corroborated by direct recordings in the monkey primary visual cortex that showed similarly fast (~40 ms) responses to grating threat CSs [41].

By contrast, multiple studies using direct recordings in the human amygdala have failed to demonstrate fast amygdala responses to emotional stimuli – latencies are consistently longer than 160 ms [42–46]. Akin to amygdala's affinity to social cues [10], fast amygdala responses to fearful faces (74 ms) have been observed in one (but no other) study, yet even that study still showed substantially lagged responses to threat scenes (186 ms) [44]. Notably, recordings in the ventral prefrontal cortex (vPFC) have shown faster responses to threat scenes at 120–160 ms [47]. Overall, the extant literature is incompatible with the standard view in terms of (i) privileged, 'quick-and-dirty' threat processing in the amygdala and (ii) the amygdala providing instructive signals for threat processing in the sensory cortex. Instead, it favors the sensory cortex for quick threat processing (Figure 1A).

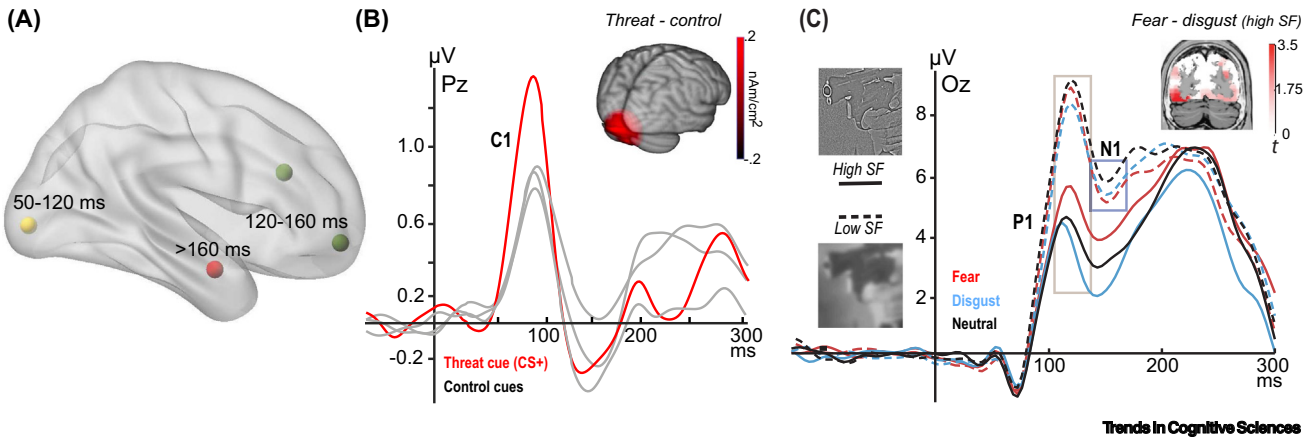

Figure 1. Fast and precise threat evaluation in the sensory cortex. (A) Among key regions in the threat network, extant data suggest that the earliest response to threat emerges in the sensory cortex (yellow dot), followed by the vPFC (green dot) and then the amygdala (red dot). (B) After threat conditioning, early electrophysiological (C1) responses were heightened selectively for the CS^+ compared to the CS^-. Importantly, the early latency (50–70 ms) and visual cortical source, combined with the manipulations of CS features (i.e., grating orientation, location, and eye specificity) targeting retinotopic neurons, highlight the primary sensory cortex as the locus of threat evaluation. Adapted from [40]. (C) Early electrophysiological (P1) responses differed not only between threat and neutral scenes but also between threat subtypes (fear and disgust). Note, this specific threat categorization was only observed with high spatial frequency/SF images (preferentially activating the cortical pathway): P1 was augmented for fear and suppressed for disgust, relative to neutral scenes (unbroken lines). This effect was further source localized to the inferior occipital cortex. With low SF images (preferentially activating magnocellular pathways), the two threat subtypes evoked overlapping, somewhat delayed threat response (N1, relative to neutral scenes; broken lines), likely informed by coarse threat processing in vPFC/orbitofrontal cortex (and potentially, the amygdala) via magnocellular pathways. These findings support the notion of fast and precise threat evaluation in the sensory cortex. Adapted from [50]. Abbreviations: CS, conditioned stimulus; vPFC, ventral prefrontal cortex.

This quick threat processing in the sensory cortex is not dirty either; it is rather precise. In contrast to gross differentiation of threat from nonthreat by the amygdala, sensory cortical threat processing is capable of fine discrimination among subordinate-level threats. To assess the specificity of this sensory processing, a series of high-density electrophysiological studies compared early visual responses to two threat subtypes (fear and disgust) contained in complex scenes [48–50]. The studies consistently demonstrated qualitatively distinct patterns for the subtypes: early visual responses (96–120 ms and source-localized to the inferior occipital cortex) were enhanced for fear and suppressed for disgust, relative to neutral scenes. Importantly, highlighting the visual cortical involvement, this specific threat processing was only observed with high spatial frequency stimuli (known to preferentially activate the parvocellular cortical pathway) (Figure 1C) [50]. By contrast, with low spatial frequency stimuli (known to preferentially activate magnocellular pathways), the subtypes elicited overlapping and delayed (~150 ms) responses, likely informed by gross threat processing in the vPFC/orbitofrontal cortex (and potentially, the amygdala) through magnocellular pathways [47,51]. Setting apart from the standard view, the sensory cortex performs a smart mode of threat processing that is not only quick but also precise.

Mechanisms of threat evaluation in the human sensory cortex

Insights from threat conditioning

How does the sensory cortex achieve such smart threat processing? The extensive literature on threat conditioning sheds important light on this question. By pairing a neutral cue (i.e., CS) with an aversive unconditioned stimulus, threat conditioning renders the CS threatening. This experimental paradigm is especially illuminating by isolating flexible, threat-specific processes, dissociable from intrinsic reflexes or physical saliency-driven responses. Furthermore, as most human threat cues are learned through experience (resulting in the virtually infinite repertoire of threat objects), threat conditioning can provide critical insights into mechanisms underlying rich, experience-dependent threat processing in humans.

Leveraging causal manipulation (e.g., lesioning, pharmacological modulation, and optogenetic and chemogenetic activation), research in animal models has identified a distributed neural network for threat conditioning, a threat network consisting of the amygdala, hippocampus, brainstem structures, basic (primary/secondary) sensory cortex, and infra- and prelimbic cortices [homologous to the human vPFC and anterior cingulate cortex (ACC)] [6,52,53]. This literature has identified rich associative plasticity in the sensory cortex that plays a crucial role in threat conditioning. Importantly, some of these plastic changes have been characterized as 'associative representational plasticity' by virtue of modifying the representation of CSs [26,54]. In humans, fMRI correlates of threat conditioning have implicated a threat network comprising similar brain areas as those in rodents [55]. Critically, in the human sensory cortex, across all modalities, associative plasticity has been reliably observed using fMRI [27–34] as well as EEG [37]. Moreover, such plasticity closely resembles that in animal models.

The sensory cortex performs stimulus encoding via ensemble neuronal responses organized through microcircuit networks across cortical layers [56]. Such microcircuit networks are modified through associative representational plasticity mentioned above, underpinning the emergence of **acquired associative representations (AARs)** of threat cues [57]. Consequently, subsequent encounters of the threat cues would activate corresponding AARs, driving fast and precise threat evaluation in the sensory cortex. Synthesizing findings in the animal and human sensory cortex, we highlight four major mechanisms of sensory coding [22,56] that are adaptable via threat conditioning to substantiate AAR of threat (Figure 2A–D).

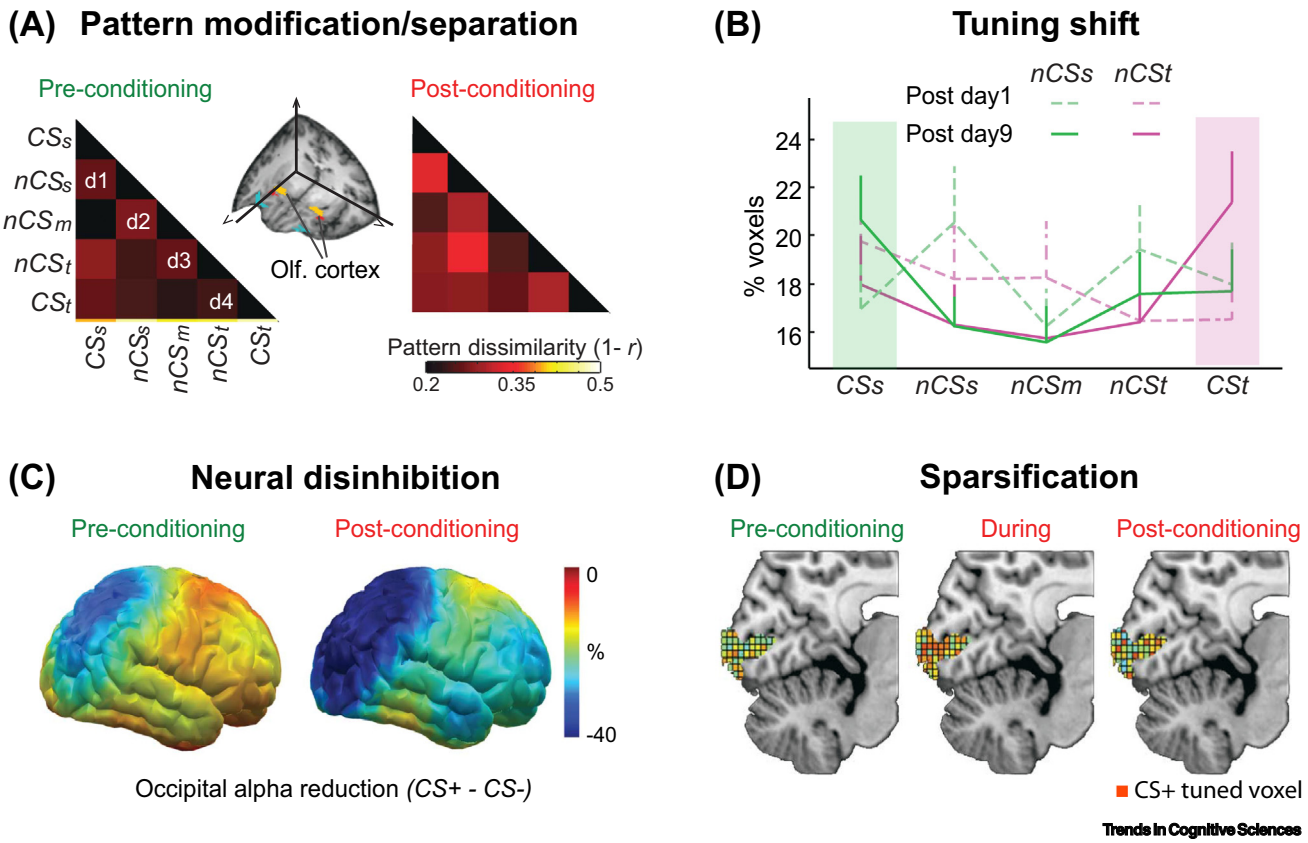

Figure 2. Mechanisms underlying threat evaluation in the sensory cortex: insights from threat conditioning. Highlighted here are four major forms of associative plasticity from threat conditioning that are established in the animal sensory cortex and observed in the human sensory cortex. Such plasticity (also known as 'associative representational plasticity' [54]) is thought to contribute to sensory cortical representations of threat cues, which would underpin threat evaluation in the sensory cortex. (A) Pattern modification and separation. Following threat conditioning, fMRI multivoxel response patterns in human olfactory cortex evinced pattern separation: increased pattern dissimilarity (d) between the CS$^+$ (CS-threat/CSt and CS-safety/CSs) and similar non-CS counterparts (nCSt and nCSs, respectively), that is, d1 and d4 (relative to d2 and d3). Adapted from [30]. (B) Tuning shift. In the same study, >20% of voxels initially identified as tuned (maximally responsive) to the nCSt and nCSs became tuned to the similar CS$^+$ (CSt and CSs, respectively) after conditioning. Reflecting its time dependency, this tuning shift was evident on Day 9 (but not on Day 1). Adapted from [30]. (C) Neural disinhibition. Following threat conditioning, CS$^+$ caused a deeper reduction than CS$^-$ in alpha oscillations at occipitoparietal sites. Given the role of alpha oscillations in inhibitory modulation of sensory cortical neuronal excitability, this alpha suppression suggests neural disinhibition in the human sensory cortex. Adapted from [61]. (D) Sparsification. The number of voxels in human V1 responsive to CS$^+$ decreased after prolonged conditioning (following a brief increase during conditioning). This finding suggests time-dependent sparsification of sensory coding ensembles. Adapted from [29]. Abbreviations: CS, conditioned stimulus; CSs, conditioned stimulus-safety; CSt, conditioned stimulus-threat.

AAR of threat in the sensory cortex

Pattern modification and separation

Ensemble neuronal responses in the sensory cortex exhibit stereotyped patterns to encode sensory cues [22,56]. Abundant animal data suggest that ensemble activation patterns in sensory cortex are modified consequent to threat conditioning [13,14]. These pattern changes may include altered composition or synaptic connectivity of a **neuronal ensemble**, as well as modified spatial and temporal activation patterns [56]. **Pattern separation** in animal sensory cortex is commonly observed in threat conditioning as ensemble activation patterns for a CS$^+$ and a (similar) CS$^-$ become distinct [13,14,22,54]. At a macroscopic level, human fMRI multivoxel pattern analysis of threat conditioning has demonstrated analogous plasticity in the sensory cortex (Figure 2A). That is, fMRI multivoxel patterns in the basic sensory (visual, auditory, and olfactory) cortex changed for the CS$^+$ [29] or became distinct between the CS$^+$ and CS$^-$ [27,30,33,34]. Importantly, increased

differentiation in multivoxel patterns is paralleled by improved perceptual discrimination of the CS^+ from similar CS^- [27,30], underscoring its behavioral relevance.

Tuning shift

Response tuning is another key mechanism of stimulus encoding in the sensory cortex [58]. A plethora of animal data has evinced that threat conditioning induces tuning shifts such that sensory cortical neurons initially not tuned to the CS^+ become optimally tuned (i.e., maximally responsive) to it after conditioning [15,54]. In the human sensory cortex, delineating tuning curves for stimuli varying parametrically along a linear dimension, an fMRI (multivoxel pattern) study [30] has demonstrated similar tuning shifts towards CS^+ (vs. the non-CS; Figure 2B). Relatedly, several human electrophysiological studies have shown sharpened sensory cortical tuning for CS^+ [59–62]. As tuning shifts alter ensemble neuronal activation, optimized CS tuning can contribute to AARs of threat CSs.

Neural disinhibition

Stimulus encoding in the sensory cortex operates upon a fine excitation–inhibition balance. Inhibitory microcircuits thus play an important role in sensory coding by modulating the excitability of primary neurons [22,25,56]. Animal work has demonstrated that threat conditioning suppresses inhibitory microcircuits in the sensory cortex, causing disinhibition of primary neurons [58,63]. In humans, recent electrophysiological studies have repeatedly demonstrated suppressed occipitoparietal alpha (8–12 Hz) oscillations in response to threat CS^+ [29,59,61,64] (Figure 2C). Given the role of alpha oscillations in inhibitory modulation of sensory cortical excitability [65–67], these findings implicate a similar disinhibition mechanism in human threat conditioning. Conversely, inhibiting the sensory cortex (with theta-burst transcranial magnetic stimulation) during threat conditioning was found to disrupt conditioned responses [68]. Therefore, neural disinhibition can contribute to AARs of threat CSs by heightening excitation of primary sensory cortical neurons and thus altering ensemble neuronal activation.

Sparsification

Sparse coding is another key mechanism in the sensory cortex [22,56,69]. Besides energy conservation, sparse coding facilitates stimulus representation by sharpening and specifying underlying microcircuit networks [69]. Animal research indicates that after initial **cortical map expansion** for the CS^+, sustained threat conditioning promotes sparser coding networks by shrinking populations of sensory cortical neurons responsive to the CS^+ [22,70,71]. Similar **sparsification** has been observed in the human sensory cortex: threat conditioning initially enlarged the extent of V1 voxels responsive to the CS^+, but following extensive training, the extent of responsive voxels decreased significantly [29] (Figure 2D). Thus, sparsification can contribute to AARs of threat CSs by sharpening and tightening its coding network [72].

In summary, multifaceted, interactive associative plasticity arises in the sensory cortex through threat conditioning. These plastic mechanisms, in concert, sculpt integrative microcircuit networks of sensory coding to substantiate AAR of threat. Accordingly, threat representations are equipped with heightened sensitivity (via tuning shift and disinhibition) and sharpened specificity (via pattern separation and sparsification), driving smart sensory threat evaluation as discussed above.

Mnemonic codes of threat in the sensory cortex

To join the threat repertoire, an acquired threat cue needs to attain long-term memory representation. Indeed, sensory cortical plasticity from threat conditioning can develop into long-term plasticity to substantiate long-term threat memory [13,14,22,54,73,74]. Importantly, this associative plasticity exhibits strong time dependence: over days or weeks, initial plasticity undergoes

progressive strengthening and specification, thereby consolidating and developing into long-term threat memory traces. Moreover, the sensory cortex has long been known as a primary site of long-term memory storage [75]. Rodent research in the past decade has shown a critical (and even causal) role of sensory cortex in the long-term storage of threat conditioning: lesioning and experimental inactivation of the (secondary) sensory cortex (across auditory, visual, and olfactory modalities) causes significant impairment in retrieval/expression of long-term threat memory [14,71,76,77].

In humans, while direct causal evidence is still lacking (Box 1 and see Outstanding questions), long-term plasticity from threat conditioning has also been observed in the sensory cortex. It also exhibits pronounced time dependence, in the form of (i) increasing strength and specificity and (ii) focal localization in the primary/secondary sensory cortex [30,78]. Specifically, as in animal models, plastic changes in human sensory cortex progress over time, becoming evident and specific after substantial delays (i.e., 9–16 days). Figure 2B shows the emergence of reliable tuning shift in the olfactory piriform cortex on Day 9 but not immediately after olfactory threat conditioning [30,78]. Additionally, the substrates of associative plasticity shifted from widespread brain areas initially to more focal, basic sensory cortices at a later stage, a pattern observed both within an experimental session with extended training [31] and between sessions 16 days apart [78] (Figure 3).

Together, extant findings suggest that threat conditioning generates lasting memory traces in the sensory cortex. Importantly, the sensory cortex likely serves as a key site of long-term repository of mnemonic threat codes [13,14], underpinning stable, enduring AAR of threat (see [79] for a review of threat engrams in the sensory cortex). Consequently, as sensory information about a threat cue reaches the sensory cortex in the initial afferent volley, it will activate these mnemonic codes/AARs (also known as threat schemata [36,80]), eliciting fast and precise threat evaluation.

Threat signaling via sensory-cortico-amygdala projection

Would the outcome of sensory threat processing be efficiently communicated to the rest of the threat network? The standard view emphasizes a thalamo-amygdala pathway for fast and coarse

Box 1. Future directions

Defining trajectories

Sensory threat representations are often acquired through experience. The standard approach of trial-averaging in cognitive neuroscience, combined with the lack of longitudinal work, has limited our knowledge about how sensory threat representations are acquired, consolidated, stored, and extinguished. Future work may fill these gaps by qualifying and quantifying temporal dynamics of neural representations, along with changing connectivity in the threat network, both throughout the experiment and over the course of subsequent days, weeks, and months.

Defining the mechanisms

While associative plasticity in the human sensory cortex closely resembles findings of the animal model, extant evidence is only correlational and relatively coarse. Future research may leverage advanced multimodal imaging and neurostimulation approaches [104,105] to refine the characterization of sensory threat representations and link them to threat engrams in humans. In addition, other learning paradigms (e.g., contextual conditioning, instrumental conditioning) may further inform the properties and underlying processes of threat representation in the sensory cortex.

Translating to fear-related disorders

To date, prevailing theories for fear-related disorders (e.g., phobias and post-traumatic stress disorder) have concentrated on the amygdala–PFC circuit. Through the lens of dysfunctional threat processing in the sensory cortex, future research may uncover a new set of pathological mechanisms (e.g., sensory cortical disinhibition [38,106]), promoting novel treatments for these disorders.

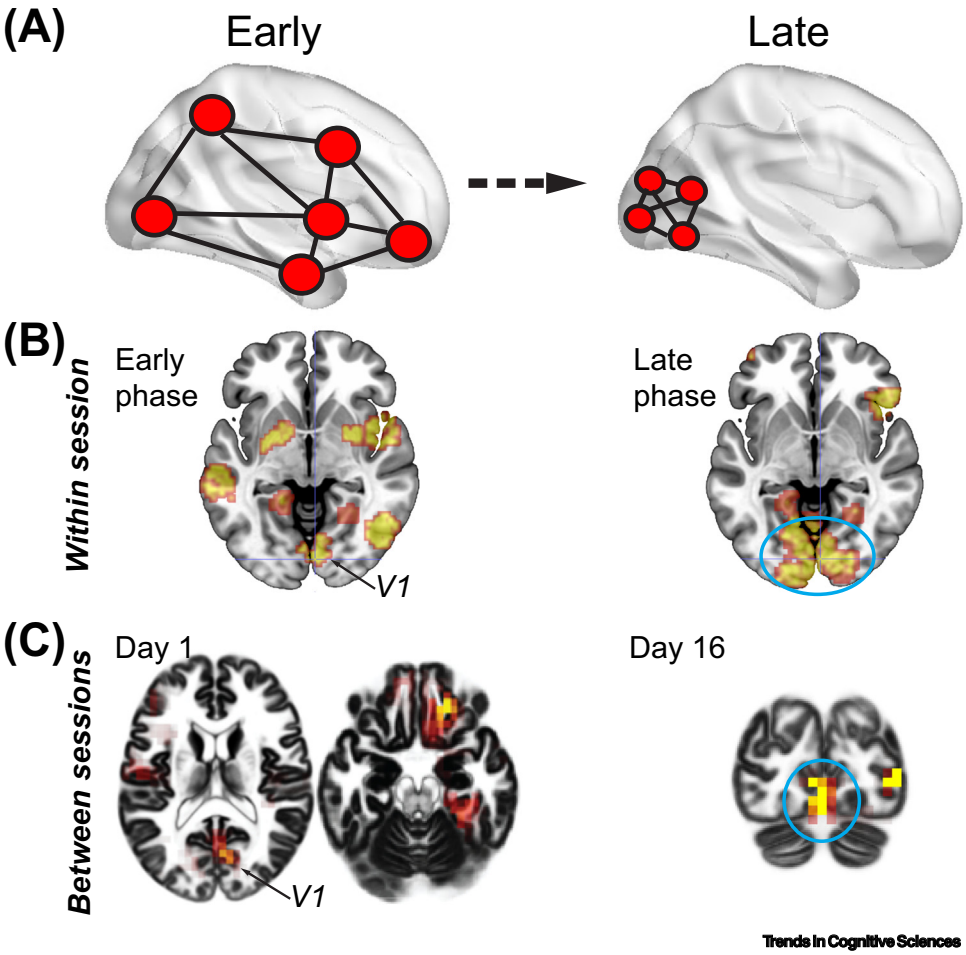

Figure 3. Evolution of associative plasticity into mnemonic threat codes in the sensory cortex. (A) Schematic of temporal trajectory. Selective responses to threat CS arise quickly (after a few trials of conditioning) in a distributed neural network [55]. Over time, these threat-specific responses become progressively localized in the sensory cortex. (B) Selective fMRI responses to CS^+ (vs CS^-) were observed in widespread areas in early trials of threat conditioning (naive state; left) and shifted to a focal locus (in the blue circle) in the visual cortex after 120 trials (formation of sensory threat memory; right). Note the accompanying enhancement in both the extent and intensity of visual cortical response to the CS^+. Adapted from [31]. (C) A similar pattern was observed in a source-level analysis of early visual evoked potentials (C1/P1, at 70–120 ms) to CS^+ (vs CS^-), extracted from high-density electrophysiological recordings. Note the long (16-day) interval between the two assessments, highlighting long-term storage of threat memory in the sensory cortex. Adapted from [78]. Abbreviation: CS, conditioned stimulus.

threat transmission. However, early rodent research had isolated the thalamo-cortico-amygdala (but not thalamo-amygdala) circuit as the principal pathway for transmitting threat signals [81]. This cortical pathway has been corroborated by multiple recent studies using advanced technologies (such as optogenetics and *in vivo* two-photon imaging). Importantly, these studies indicate that sensory cortical projections to the amygdala play a critical and even causal role in the long-term expression of threat conditioning [74,77,82,83].

There has been limited research into the sensory cortex-to-amygdala pathway in human threat conditioning. Nonetheless, it is reasonable to assume that the important function of this cortical pathway is conserved in humans. In support of that idea, a graph-theoretical analysis of magneto-encephalography data showed that during threat conditioning, limbic areas became disconnected

while the primary visual cortex (V1) took on a central role (as a central hub) in the brain's overall network organization [84]. In addition, an fMRI study modeled causal information flow between sensory and limbic areas and demonstrated that projections from the sensory cortex to the amygdala drove negative perception induced by an anxious state [85]. Convergent evidence can also be found in a new fMRI study that highlighted sensory cortical interaction with the amygdala and hippocampus in (declarative associative) threat memory [86]. It is thus plausible that threat decoded in the sensory cortex is relayed as an instructive signal to the amygdala and other areas for elaborate, network-wide threat processing.

A sensory account of threat processing

The literature reviewed above indicates that the basic sensory cortex contains the necessary microcircuit architecture for analysis beyond physical features, enabling threat evaluation that is both fast and precise. Mechanistically, the sensory cortex stores long-term mnemonic representations of threat, sculpted through aversive experiences, to encode environmental threat. The resulting threat-imbued sensory afferent sweeps elicit downstream threat processing in the amygdala and other areas of the threat network. These ideas thus motivate a sensory account of threat processing, involving initial threat evaluation in the sensory cortex (Stage I), intermediate threat processing in the distributed threat network (Stage II), and advanced threat processing across multiple large-scale brain networks (Stage III; Figure 4). This chronometry tracks previous neural models [87,88] and classical cognitive models of emotion processing [80,89]. In addition, combining psychophysics and neurometric modeling over a linear continuum of fear intensities, a recent electrophysiological study decomposed threat operations (e.g., categorization, detection, valuation, and conscious perception) and their temporal profiles, conferring direct empirical support for such chronometry [90].

Stage I (sensory cortical threat encoding)

The sensory cortex is the primary target of environmental input and accordingly, the primary site of sensory coding. Beyond rudimentary processing in the periphery and thalamus [16,17], the sensory cortex merges multiple inputs and conducts combinatory coding of sensory features and threat value (as integrated in the AAR). This stage of sensory cortical threat encoding is responsible for smart (fast and precise) initial evaluation of environmental threat (e.g., threat categorization and qualitative detection [90]), which is relayed to downstream limbic and brainstem structures to trigger Stage II.

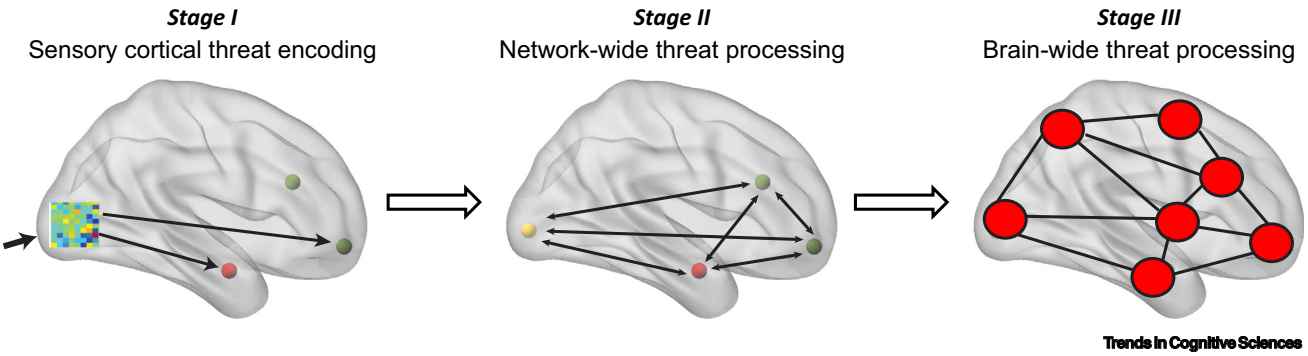

Figure 4. A sensory account of threat processing. Schematic of a sensory account of threat processing. Stage I (sensory cortical threat encoding): mnemonic codes (i.e., long-term acquired associative representation) of threat in the sensory cortex (threat schemata) are activated by environmental input, eliciting initial threat evaluation as early as the sensory feedforward sweep. Stage II (network-wide threat processing): sensory afferents carrying threat signals reach the amygdala, the salience network, and other areas of the threat network, activating interactive, network-wide threat processing. Stage III (brain-wide threat processing): identification of significant threat leads to a 'global ignition', activating broad, large-scale networks to support goal-directed, conscious threat processing and response.

Stage II (network-wide threat processing)

Threat-imbued sensory projections terminate in major limbic areas (the amygdala, hippocampus, and insula) and (directly and indirectly) interact with brainstem structures (e.g., locus coeruleus, periventricular thalamus, and periaqueductal gyrus), activating the salience network (including anterior insula and dorsal ACC) and subsequently the entire threat network (including vPFC). Via bidirectional interactions across the constituent nodes, waves of threat information reverberate over widespread circuits, permitting multifaceted, associative analysis of the signal. This stage supports elaborate (but constrained) threat processing (e.g., quantitative threat detection and valuation [90]).

Stage III (brain-wide threat processing)

With the identification of significant threat, the brain enters a state of 'global ignition', activating multiple additional large-scale networks, particularly, the executive control network (e.g., the dorsolateral PFC and parietal cortex) and motor network. This stage engages multiple, coordinated processes, supporting subjective feelings (e.g., conscious appraisal and interpretation [90]) and voluntary, goal-guided responses (e.g., emotion regulation and motor action) [91].

While emphasizing the sensory cortex in initial threat evaluation, this model is embedded in a distributed network of threat processing. It features the amygdala in Stages II and III, which is consistent with its relatively slow response latency (as reviewed above) and lesion evidence of impaired threat processing on intermediate to high levels (e.g., conscious perception and appraisal) but not the low level (e.g., automatic relevance detection/categorization) [92–95]. Furthermore, Stages I and II can both be characterized as preconscious [96] and be activated by subliminal cues. Thus, this model accommodates the notion that early visual cortical threat evaluation elicited by subliminal cues [97–99] may drive subliminal amygdala threat responses [100–102].

Concluding remarks

Efficient threat processing is essential for survival. The sensory cortex has participated in this process since the ancestral amniote. Influential frameworks such as the amygdala-centric view (and related triune brain theory [103]) have made important contributions to our inquiry into threat processing in the brain, but they have also become limiting as this quest continues to advance. We propose to expand the scope of threat theories to emphasize initial threat evaluation arising from sensitive, specific, and experience-dependent threat representations that reside in the sensory cortex. This sensory cortex-based threat evaluation is consequently both fast and precise and can support multiple functions (e.g., threat detection, discrimination, categorization, and bottom-up attention), in the service of optimized threat responses. While drawn primarily from classical threat conditioning, this sensory model can be applied to additional forms of learning (e.g., contextual conditioning, instrumental conditioning). AAR emerging through these extra learning circuits (e.g., hippocampus, striatum) can add to the complexity of threat representation in the sensory cortex (Box 1). Finally, rather than returning to a corticocentric framework, the model is founded on a distributed network of cortical and subcortical structures. To conclude, we hope that this model prompts new questions and novel investigations (Box 1 and see Outstanding questions) and sheds light on a hitherto underappreciated system, ultimately helping to account for the impressive repertoire of adaptable, complex, and dynamic threat responses in humans.

Outstanding questions

To what extent are threat-related plastic changes observed in human sensory cortex causal in threat processing and hence reflective of threat engrams? Causal inquiries are increasingly feasible in human research owing to rapid advances in noninvasive brain stimulation, which, combined with multimodal neuroimaging, may shed direct light on this question.

How does initial plasticity in the sensory cortex evolve over time into long-term plasticity? What is the temporal profile of such plasticity (over minutes, hours, days, and months): are there distinct stages and critical periods through this evolution, and what is their respective functional relevance (e.g., learning, consolidation, storage, and extinction)? Expanding laboratory research beyond immediate and short-term learning into defining long-term effects not only addresses important theoretical questions but also holds promise for translation into clinical and real-world applications.

What is the topological organization of the human threat network? What are the temporal dynamics of the network organization, and what is the functional relevance of network reorganization at different stages? Beyond the identification of distributed brain regions, knowledge of the threat network organization and reorganization over time would afford novel insights into threat representation and processing.

How do the sensory mechanisms vary with individual differences (e.g., trait and state anxiety) and deviate in patients with disorders along the anxiety, fear, and stress spectrum [e.g., post-traumatic stress disorder (PTSD)]? Answers can inform the genesis and maintenance of these disorders.

Can neuromodulatory technologies be used to weaken or even erase threat memories, by virtue of modifying or removing threat representations in the sensory cortex? Such interventions, especially via noninvasive brain simulation that is generally safe and accessible, may open a new line of treatment for fear disorders such as PTSD.

Declaration of interests

No interests are declared.

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