# 3 Perceptual Mechanisms of Anxiety and Its Disorders

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The ability to minimize contact with aversive events is a hallmark of adaptive behavior, among which the ability to quickly detect danger and initiate an immediate response can mean life or death. Anxiety, characterized by an overactive defense system, often exaggerates threat processing to the extent that significant functional impairment occurs (Barlow, 2002; Gray & McNaughton, 2000; Lang et al., 2000). Research in the past few decades has characterized an array of cognitive biases to threat in anxiety, in domains of attention, memory, interpretation, emotional association, and inhibitory control (Mathews & Macleod, 1994, 2005). However, biases in sensory perception, a fundamental cognitive operation, have not been well recognized in anxiety research. From an evolutionary perspective, it is conceivable that the sensory system, where an environmental cue first registers with an organism, is endowed with the capacity to categorize motivational significance of the stimulus, optimizing the animal's response with no delay (Li, 2014; Weinberger, 2007). Given that sensory perception constitutes one of the first operations in the cognitive stream, biased sensory perception of threat would influence downstream processes, directly or indirectly contributing to a variety of cognitive and emotional anomalies observed in anxiety. This chapter is thus dedicated to sensory perceptual mechanisms of anxiety with the hope to shed light on this crucial but so far overlooked aspect of anxiety pathology.

As reviewed in what follows, dominant theories of anxiety have conceptualized threat processing into a framework of three primary stages and systems. Importantly, the first stage of this framework is characterized by basic, sensory processing of environmental stimuli, "tagging" the stimuli with "threat codes" and triggering elaborate threat analysis in the later stages. In essence, this first stage represents sensory perception of threat, but presumably, the early and brief nature of this sensory stage has rendered it obscure from behavioral observations, leaving sensory perception of threat still poorly understood. Toward that end, this chapter garners evidence from neuroscience research that has gained remarkable access to this otherwise elusive stage.

In clinical conceptualization, the term *perception*, or *threat perception* specifically, can describe abstract ideas or views such as perception of health risks or perception of social tension, which heavily engages higher-order processes such as appraisal and reasoning. Here, in reference to basic mechanisms of fear and anxiety, in particular sensory perception of threat, the term *perception* pertains

specifically to the processes that organize and translate sensory input (e.g., light, sound, odor) from the environment into concrete sensory experiences (i.e., percepts) such as the perception of an angry face or a frightened and screaming crowd.

This chapter starts with a survey and synthesis of dominant, influential theories of information-processing biases in anxiety. As these theories were largely constructed on behavioral data, neuroscience findings are then discussed to furnish empirical support to these models. This chapter then proceeds with neural data providing mechanistic insights into sensory perception of threat and related anomalies in anxiety, and ends with a proposal of a neurosensory model of anxiety pathology.

## Summary and Synthesis of Dominant Information-Processing Models of Anxiety

Experimental psychopathology research in the past few decades has generated a voluminous literature on information processing in anxiety. Phenomena of anxiety-related biases to threat in various cognitive domains, such as detection, attention, interpretation, and expectation, have been ably summarized and synthesized in excellent reviews and meta-analyses (Armstrong & Olatunji, 2012; Beard & Amir, 2010; Cisler & Koster, 2010; McNally, 1995; Ouimet et al., 2009; Staugaard, 2010; Sussman et al., 2016; Van Bockstaele et al., 2014; Williams et al., 1996). Based on this literature, several influential theoretical models of anxiety have been proposed to isolate and describe critical cognitive systems underlying vulnerability to and pathology of anxiety. In spite of certain disparaging terminology and nuances, these models, some older and classical, some newer and integrative, largely converge on a sequence of automatic and strategic processes unfolding over time (as reviewed later in this chapter and also in Bar-Haim et al., 2007; Mathews & Mackintosh, 1998; Van Bockstaele et al., 2014). Building on their consensus, we synthesized these models into an integrative information-processing account of anxiety, where the relevant cognitive processes were organized and streamlined into three primary stages (Figure 3.1A).

### The Schema-Based Theory of Beck and Colleagues (1985, 1997)

Beck and colleagues proposed a three-stage, schema-based information-processing model, where the first and third stages are biased in anxiety, resulting in "erroneous or biased interpretation of stimuli as dangerous or threatening" as a core feature of anxiety disorders (Beck & Clark, 1997; Beck et al., 1985). Stage I – initial registration – involves rapid, automatic stimulus processing. By automaticity, this stage is characterized by low-level parallel processing that operates outside consciousness and volition and is capacity-free.

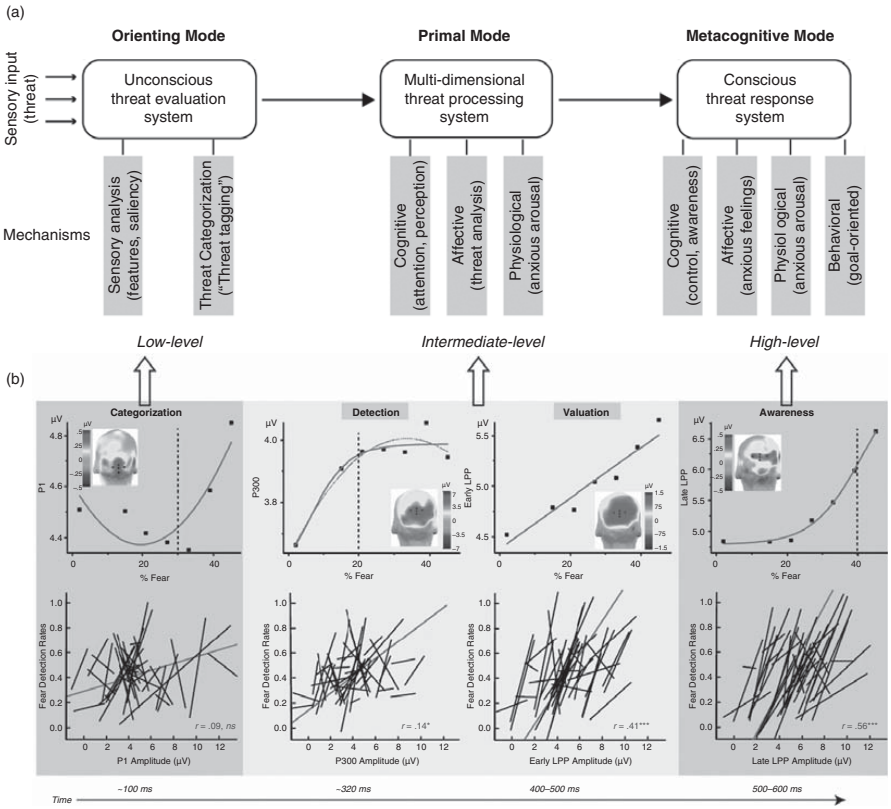


**Figure 3.1** *A synthesized psychological model of anxiety. (A). A synthesis across several dominant cognitive models of anxiety yields a three-stage model, composed of an early "orienting mode," an intermediate "primal mode," and a late "metacognitive mode." (B). Psychometric and neurometric modeling of fear detection performance and ERPs in a fear detection task maps out four key operations unfolding in sequence, which align nicely with the three-stage model of anxiety. The open arrows point the key operations to the three stages in (A).*

These processes are more "perceptually" than "conceptually" driven. The first stage is also referred to as the "orienting mode." Anxious orienting would facilitate threat detection, which triggers Stage II – immediate preparation, also known as the "primal mode." This second stage is characterized by a rigid, reflexive set of affective, cognitive, behavioral, and physiological responses that constitute a state of anxiety, including (a) autonomic arousal, (b) negative thoughts, (c) avoidance behavior, (d) fearful emotions and feelings, and (e) hypervigilance for threat cues. Stage III – secondary elaboration, also known as the "metacognitive mode" – is represented by strategic, higher-order information processing. Anxiogenic schemas would bias this processing to generate anxious interpretations and maladaptive coping behavior.

### The Information-Processing Model of Williams et al. (1988, 1997)

Williams and colleagues postulated that two distinct pre-attentive processing stages are relevant to anxiety (Williams et al., 1988, 1997). The first stage involves the evaluation of threat value of a stimulus through an "affective decision mechanism" (ADM). Similar to Beck and colleagues' orienting mode, this ADM engages parallel processing over a distributed network and is automatic ("pre-attentive"). High levels of *state anxiety* can amplify threat value output from this stage. If the threat value output is sufficiently high, the second stage will be activated, which involves the "resource allocation mechanism" (RAM) regulating cognitive resources, especially attention. This stage resembles the primal mode in Beck and colleagues' model. The RAM is subject to the influence of *trait anxiety*, prompting high trait-anxious individuals to show vigilance to threat and low trait-anxious individuals to display avoidance of threat. Furthermore, stressful contexts or elevated state anxiety would exacerbate the biases of the RAM in trait-anxious individuals.

### The Emotion Activation Model of Ohman (1993, 2000)

Ohman's emotion activation model consists of three main stages – feature detection, significance evaluation, and conscious threat perception (Ohman, 1993, 2000). Similar to Beck and colleagues' first stage of initial registration, an external stimulus first registers with the "feature detectors" in a nonconscious, automatic fashion. These detectors isolate signal features of biologically significant stimuli, which then triggers the unconscious "significance evaluator." Confirmation from the significance evaluator turns on the third stage: controlled, strategic processing of the stimulus, generating conscious threat perception. Notably, Ohman's model also emphasizes that autonomic arousal is directly activated by feature detectors, which provides input to facilitate significance evaluation and conscious threat perception. A central and somewhat unique concept of this model is that preliminary, unconscious analysis of basic stimulus features is enhanced in anxiety, which shifts subsequent cognitive processes such as attention to favor threat information.

### The Cognitive-Motivation Model of Mogg and Bradley (1998)

Mogg and Bradley proposed a cognitive-motivation model consisting of two stages – a valence evaluation system (VES) and a goal engagement system (GES) (Mogg & Bradley, 1998). The VES resembles the ADM in Williams and colleagues' model, although the VES is susceptible to *trait anxiety* in contrast to the ADM, which is susceptible to *state anxiety*. Mogg and Bradley argued that trait-anxious individuals are prone to tag relatively innocuous stimuli as threat. Threat output is then fed into the GES, similar to the RAM in Williams et al. (1988, 1997), which interrupts ongoing (non-threat-relevant) goals and prioritizes threat processing. Therefore, the hypersensitive VES in anxiety can lead to the hyper-reactivity

of the GES, resulting in affective, cognitive, and behavioral anomalies. This model emphasizes a lowered threshold in anxiety for identifying *minute* environmental threat and argues that attentional biases to threat in anxiety are rather a passive consequence of the former.

### The Selective Processing Model of Mathews and Mackintosh (1998)

This model concerns primarily how threat intervenes with the processing of none-motional stimuli, as observed in the emotional Stroop task, which is especially salient in anxious individuals (Williams et al., 1996). Mathews and Mackintosh posited that stimuli are first evaluated via a threat evaluation system (TES), and threat output from this system turns on threat-relevant "distractor representation," which disrupts non-threat "target representation" (Mathews & Mackintosh, 1998). Here, Mathews and Mackintosh further introduced the idea of "voluntary task-related effort," such that higher-level cognitive control is triggered by the TES output to inhibit and override interference due to the distractor. The extent of biases in information processing and behavioral output lies in the balance of the TES and the voluntary control system. Similar to the notions of ADM (Williams et al., 1988, 1997), significance detectors (Ohman 1993, 2000), and VES (Mogg & Bradley, 1998), anxiety enhances threat analysis by the TES and intensifies its activation of distractor representation.

### The Integrative Attention Model of Bar-Haim et al. (2007)

Building on previous models, primarily Williams et al. (1988, 1997) and Mogg and Bradley (1998), Bar-Haim and colleagues proposed a four-stage integrative model of attentional biases. The model starts off with a pre-attentive threat evaluation system (PTES), which tags a potential threat stimulus with high threat value (Bar-Haim et al., 2007). In consequence, the PTES transitions into a resource allocation system (RAS), which sets off an anxious state of physiological arousal, attentional biases, and anxious feelings. With that, a guided threat evaluation system (GTES) ensues, turning on a set of strategic operations, including context- and memory-based cognitive appraisal and coping assessment. Finally, the entire process concludes with a GES, prompting goal-oriented behavior. If the GTES evaluates the threat to be low, the GTES will provide inhibitory feedback to the PTES and RAS. In contrast, if the GTES confirms the threat alert by the PTES, a full-blown state of anxiety is likely to follow. As Bar-Haim and colleagues emphasize, anxiety could intensify threat processing at all four stages.

### A Synthesis of Dominant Models

As has probably become evident to the reader, these dominant models of information processing in anxiety overlap substantially. Although the numbers of main stages differ somewhat, ranging from two to four, these six models agree on two

primary systems: a *threat evaluation system* that is largely pre-attentive or unconscious, and a delayed *goal-oriented processing system* that is largely conscious and voluntary. In between these two stages, some models postulate additional stages, concerning intermediate processes in multiple dimensions (i.e., affective, cognitive, and physiological). This middle stage is characterized by resource allocation processes, which distribute cognitive resources to threat information, often at the cost of disrupting task-related or ongoing processes that are not threat-relevant.

In order to organize and streamline the processes implicated in these dominant models, especially along the time course delineated by brain electrophysiological evidence (reviewed later in this chapter), we provide a synthesis of these models. An effort is also made to apply relatively standard terms in cognitive psychology and neuroscience to the implicated mechanisms and processes. Our synthesis results in three main stages and systems of threat processing (Figure 3.1A). We borrowed the terms used by Beck and colleagues (Beck & Clark, 1997; Beck et al., 1985) for the succinct abstraction of the stages, ensuing the onset of a threat stimulus: (1) the orienting mode, (2) the primal mode, and (3) the metacognitive mode.

In terms of cognitive operations, the orienting mode is characterized by low-level, unconscious threat evaluation, involving specific mechanisms of basic sensory analysis of stimulus features, such as features signaling threat (Ohman 1993, 2000) and coarse, broad categorization of threat (vs. non-threat), such as threat tagging proposed in multiple models. Anxiety can bias the orienting mode to threat by increasing signal detection sensitivity or lowering threat threshold such that minute threat will be detected. The orienting mode is brief, and once threat is tagged, the primal mode starts to unfold. The primal mode, the main stage of information processing, is characterized by preconscious, intermediate-level, multidimensional threat processing, evoking interactive cognitive, affective, and psychological processes. Processes in different domains work in concert to efficiently allocate resources to prioritize threat processing. Mechanisms in this stage include selective attention, intermediate-level perception, progressively elaborate threat evaluation, and autonomic arousal. Anxiety can bias the primal mode by allocating cognitive resources heavily to threat information. For example, anxiety can heighten selective attention to threat and amplify autonomic arousal, which further fuels threat prioritization. Finally, the primal mode gives rise to the third stage, the metacognitive mode. Characterized by conscious threat responses, this mode involves high-level, voluntary, goal-guided, and motivationally meaningful responses. Mechanisms engaged in this stage include conscious perception, strategic deployment of attention, conscious experience of feelings, and sustained arousal. Goal-oriented behavior will occur (e.g., avoidance) in this stage. Anxiety can bias the metacognitive mode by negatively altering interpretation and appraisal, disrupting top-down effortful control, and exaggerating defensive behavior.

In summary, several influential models were generated from a voluminous body of work. However, this body of work comprises almost exclusively behavioral observations (besides relatively simple physiological measures such as eye

tracking and skin conductance responses), and many of the models were proposed prior to the "neuroscientific revolution" of emotion and anxiety research. It thus begs the question as to how these models fare in comparison to findings from the neuroscience field.

## Threat Processing in the Brain

### Neural Mapping of the Threat-Processing Stages

A remarkable fact, as reviewed in what follows, is that these brilliant and, to some extent, intuitive models have closely mapped onto empirical, neuro-electrophysiological delineations of the different processes and stages of threat processing. Starting from the two-stage model of early "quick-and-dirty" and delayed elaborate processing of threat information (LeDoux, 1995), this literature has expanded to support a complex system involving multiple stages and processes, mediated by distributed, parallel neural pathways (Adolphs, 2002b; Pessoa & Adolphs, 2010; Vuilleumier & Pourtois, 2007).

Akin to these neural models of emotion processing, brain electrophysiological (mainly event-related potential [ERP]) research has leveraged its precise temporal resolution to delineate the time course of information processing of emotional stimuli on the scale of milliseconds. Findings from this research implicate three temporal stages of emotion processing (cf. Adolphs, 2002b; Miskovic & Keil, 2012; Olofsson & Polich, 2007; Vuilleumier & Pourtois, 2007). The first stage, indexed by the P1 component (a visual ERP that appears at ~100 ms), represents sensory processing of emotional stimuli in the low-level, occipital visual cortex. The second stage, indexed by the N1/N170 components (onset ~170 ms), entails intermediate-level, configural perceptual analysis in the temporal visual cortex. The third stage, indexed by the P3/P300 and late positive potential (LPP) components (~300 ms and beyond), reflects high-level, cognitive, and motivational processes. During this stage, emotion processing engages memory-based, goal-oriented operations, often culminating in conscious perception of the stimuli and volitional behavioral response. Broadly speaking, this sequence of electrophysiological events corresponds really closely to the three main stages of the cognitive models presented earlier in this chapter.

Pertinent to the perception of threat specifically, a recent study in our lab acquired fear detection rates and ERPs to parametrically varied levels of fearful expressions along a morphing continuum (Forscher et al., 2016). To provide further insights into the specific cognitive mechanisms involved at different stages in threat perception, we decomposed threat processing by combining psychometric and neurometric modeling. Building on the psychometric curve marking fear perception thresholds (e.g., detection, sub- and suprathreshold perception), neurometric model fitting identified four key operations along the information-processing stream (Figure 3.1B). Unfolding in sequence following face presentation, these

four psychological processes are: (1) swift, coarse categorization of fear versus neutral stimuli (~100 ms, indexed by the P1); (2) detection of fear by picking up minute but psychologically meaningful signals of fear (~320 ms, indexed by the P3); (3) valuation of fear signal by tracking small distances in fear intensity, including subthreshold fear (400–500 ms, indexed by an early subcomponent of the LPP); and, lastly, (4) conscious awareness of fear, supporting the visibility of suprathreshold fear (500–600 ms, indexed by a late subcomponent of the LPP). Furthermore, as the processes became progressively refined over time, they were also increasingly linked to behavioral performance (i.e., fear detection rates; Figure 3.1B, bottom row). Specifically, from the first to the last operations, within-subject brain–behavior association grew from no association, to weak, then moderate, and finally strong, respectively.

Overall, these findings provide specific descriptions and temporal profiling of threat processing stages. The first operation – broad threat-non-threat categorization – would correspond to the orienting mode in threat processing, which automatically tags the stimuli as threat or non-threat. Such gross categorization (at the P1 window) concurs with standard object categorization (e.g., natural vs. domestic scenes) (Thorpe, 2009). This finding also aligns with the notion that emotional stimuli can elicit rapid emotion categorization based on automatic, bottom-up sensory input (Brosch et al., 2010; Young et al., 1997), coinciding with Ohman's idea of "feature detectors" that isolate threat-relevant signal features (Ohman 1993, 2000). This significance detection then activates salience-driven, bottom-up attention and the brain's salience network, which switches on other networks to start resource allocation (via attention and working memory) and goal-driven processes in the subsequent stages (Corbetta & Shulman, 2002; Menon & Uddin, 2010; Seeley et al., 2007).

The second and third operations – threat detection and valuation – would largely fall into the primal mode as the intermediate-level threat analysis. As illustrated in Figure 3.1B, the neural detection threshold aligns with the inflection point (25% fear) of the psychometric function, and the strength of this neural response was significantly (though only weakly) predictive of fear detection rates, suggesting somewhat reliable threat detection at this stage. The third operation is more sophisticated and advanced, linearly tracking the intensity of fearful expressions and directly predicting behavior performance ($r = 0.41$). The last operation brings about conscious awareness, corresponding closely to the metacognitive mode, where consciousness of threat emerges and conscious processes ensue. In keeping with that, this last operation accounts for a remarkable 31% of the total variance of the behavioral output.

Compared to the later operations (especially threat valuation and awareness), the first operation (threat tagging) does not show a relation with the behavior. This finding underscores the notion made earlier in this chapter that the orienting mode is likely to be elusive to behavioral observation. Many creative paradigms (e.g., emotional Stroop, dot-probe, visual cueing, and visual search) have been used to isolate early operations in threat processing, but as pointed out early in the chapter,

behavioral measures from these tasks are inevitably confounded by operations from multiple stages (McNally, 1995). By virtue of rapid development of neuroscientific methods, especially brain electrophysiology technologies, relatively pure measures of the orienting mode have become viable.

## Early Neural Response to Threat

Neuroimaging (fMRI and PET) studies and meta-analyses have provided compelling evidence that threat (relative to neutral) information leads to greater activation in the visual system, including primary (V1) and associative (e.g., fusiform, lateral occipital) visual cortices (Adolphs, 2008; Lang et al., 1998; Lindquist et al., 2012; Phan et al., 2002; Phelps, 2006; Sabatinelli et al., 2013; Trautmann et al., 2009; Vuilleumier et al., 2003; Vuilleumier & Pourtois 2007). Whereas attention strongly modulates activity in visual cortices, potentially mediating the threat-related augmentation of visual activity (Pessoa et al., 2002, 2003), preferential threat perception can also operate independently of attention (Phelps, 2006; Vuilleumier et al., 2001) and outside of conscious awareness (Morris et al., 1998, 2001; Pessoa et al., 2005). Nevertheless, in terms of disentangling the multiple processes and stages in threat processing, neuroimaging research appears to be facing a similar conundrum that has confronted behavioral research. That is, as late processing also activates low-level sensory cortices (Foxe & Simpson, 2002), it is unclear whether these effects reflect early basic sensory perception or the complex end stage where multiple information streams bind to form a final percept of threat.

By contrast, with its superior temporal resolution, brain electrophysiological research has a unique technical advantage in this regard. In particular, the P1, arising from the extrastriate cortex around 100 ms post stimulus, has proven very useful in indexing early visual perception (Gomez Gonzalez et al., 1994; Mangun et al., 1993; Morris & Dolan, 2001). Work from our laboratory and others' has demonstrated enlarged P1 in response to threat than non-threat stimuli, and intracranial source estimation has confirmed the sources of P1 threat response in the occipital cortex, including the extrastriate and occipital fusiform cortices (Eimer & Holmes, 2007; Holmes et al., 2008; Krusemark & Li, 2011, 2013; Li et al., 2008b; Li et al., 2007; Pizzagalli et al., 1999; Pourtois et al., 2004, 2005; Wieser et al., 2012; You & Li, 2016).

Recently, a series of studies examining ERPs to fear and disgust (vs. neutral) stimuli (scenes or faces) have indicated divergent processing of fear and disgust during early sensory perception: relative to neutral stimuli, fear stimuli enhance whereas disgust stimuli suppress the P1 response (Krusemark & Li, 2011, 2013; Liu et al., 2015; You & Li, 2016). These intriguing P1 response patterns were consistent across various tasks and contexts, and importantly, they were incompatible with the arousal levels of these emotions (i.e., fear > disgust > neutral), thereby excluding confounds of arousal and arousal-related attention and emphasizing basic sensory encoding of these threat stimuli. In addition, this differentiation of fear and disgust in early sensory processing also raises the question whether the

coarse significance detection during early sensory processing operates along the dimension of threat-versus-non-threat or the dimension of approach-versus-avoidance (as fear elicits immediate approach while disgust immediate avoidance (Adolphs, 2002a). Or, this significance detection process is "smarter" than we think. At any rate, future research is needed to shed more light on this process.

Furthermore, the P1 component precedes the onset of the N170 component, which arises around 170 ms and reflects feature configuration and object identity (e.g., face) categorization (Bentin et al., 1996; Eimer, 2000; Vlamings et al., 2009). The fact that the P1 occurs before configural object representation helps to isolate these P1 effects to low-level sensory processes (e.g., "feature detectors") that define the orienting mode. In keeping with that, single-unit recording data in the macaque temporal cortex demonstrated rapid emotion discrimination prior to face identification (Sugase et al., 1999). Strikingly, recent work has demonstrated that threat can enhance the C1 component, one of the first visual evoked potentials arising ~50–70 ms in the primary visual (V1) cortex (cf. Miskovic & Keil, 2012), pushing threat processing even earlier and lower-level in the information-processing stream. In sum, electrophysiological data provide support that threat processing takes place as early as the initial sweep of sensory processing (Vuilleumier & Pourtois, 2007), underlying the orienting mode characterized by fast, automatic, low-level sensory processing of threat stimuli.

## Early Neural Response to Threat in Anxiety

How does anxiety influence this early sensory processing of threat? fMRI data have revealed enhanced visual (Åhs et al., 2009; Etkin & Wager, 2007; Lipka et al., 2011; Paquette et al., 2003; Straube et al., 2005) and olfactory cortical activity (Krusemark & Li, 2012; Krusemark et al., 2013) in response to threat in anxious patients and individuals. Again, as mentioned earlier, the sluggish fMRI response does not permit the disentanglement of early, low-level activity from later, higher-order activity in the sensory cortex. Nevertheless, ERP evidence, especially based on early visual ERPs such as the P1 and C1, has amassed to address this question.

Reflecting enhanced early visual processing of threat in anxiety, threat (vs. neutral or positive) stimuli (e.g., faces, words, and pictures) elicit augmented P1 and C1 responses in anxious individuals, including both clinical and nonclinical groups (Eldar et al., 2010; Holmes et al., 2008; Krusemark & Li, 2011; Lee et al., 2017; Li et al., 2008b; Li et al., 2007; Mueller et al., 2009; Rossignol et al., 2013; Sass et al., 2010; Venetacci et al., 2017; Weinberg & Hajcak, 2011). Using bimodal (visual and olfactory) threat presentation, a study further demonstrated that trait-anxious individuals are particularly adept at integrating bimodal threat cues to improve early visual processing of micro-fear expressions (12% fear) (Forscher & Li, 2012). Administering cortisol one hour before the test, van Peer and colleagues observed enhanced P1 to angry (vs. happy) faces in both high trait-avoidant individuals (van Peer et al., 2007) and patients with social anxiety disorder (van

Peer et al., 2009), highlighting a close relationship between this heightened early threat processing and stressful arousal in anxiety.

That said, an intriguing finding from this literature is that in other studies, anxious individuals exhibit a broad, nonspecific (vs. threat-specific) enhancement of early visual processing. Spider phobics show elevated P1 and C1 responses to images of spiders and non-phobic objects (e.g., flowers and butterflies), relative to the control group (Michalowski et al., 2009, 2014, 2015). In addition, socially anxious individuals exhibit enhanced P1 and C1 responses to all faces, regardless of their expressions (Helfinstein et al., 2008; Kolassa & Miltner, 2006; Kolassa et al., 2007, 2009; Mühlberger et al., 2009; Peschard et al., 2013; Rossignol et al., 2012a, 2012b; Wieser & Moscovitch, 2015). Similarly, individuals with high trait anxiety also show a general P1 augmentation to all faces relative to non-face images (Walentowska & Wronka, 2012).

Faces are probably inherently salient, emotion-relevant stimuli such that even "neutral" faces would be emotionally charged due to its race, gender, or eye gaze, thereby attaining preferential perception compared to other objects (cf. Farah et al., 1998) and reliably activating the amygdala regardless of emotion (Johnson, 2005). It is thus plausible that in early sensory analysis, anxious individuals are particularly tuned to faces, even "neutral" ones, due to the inherent emotional salience. Another explanation for the general P1 enhancement to faces is that a threat-relevant context is elicited by threatening faces (e.g., fearful or angry) among socially anxious individuals, which generates a broad amplification of early sensory processing of all images presented in that context. Consistently, the presence of spider images amidst other images (even positive images) sets up a threatening context among spider phobics, which in turn exaggerates early sensory processing. A third possible explanation holds that there is a general, threat-neutral exaggeration of basic sensory processing, akin to the notion of hypervigilance. This idea is explicated in depth later in this chapter.

## Mechanisms Underlying Early Threat Processing

How does such fast threat processing arise in the sensory cortex? Traditional theories of cortical organization hold that the primary sensory cortex (e.g., the V1 cortex) deals rather exclusively with sensory analysis of environmental inputs, and association cortices (e.g., the extrastriate cortex) interpret the primary cortical output into object percepts (i.e., "visual psychic," e.g., color and shape) (Campbell, 1905; Leipsic, 1901). In parallel to this sensory modular view or the "sensory module," a "threat/fear module" exists, according to traditional views (Fodor, 1983; Tooby & Cosmides, 1992). As promoted by the influential review by (Ohman & Mineka, 2001) and echoed by (LeDoux, 2012), threat processing arises from a selective, automatic, and encapsulated module, which is underpinned by a specialized neural circuitry. This fear circuitry centers around the amygdala and extends onto other limbic regions such as the hypothalamus and hippocampus (see reviews by Davis,

1992; Fanselow, 1994; Kapp et al., 1992; Lang et al., 2000; LeDoux, 2000; Panksepp, 1982). According to this view, environmental input from midbrain and thalamic nuclei can directly turn on this fear circuitry and the entire encapsulated fear system. Output from the amygdala then relays emotionally charged information of the stimulus to the sensory cortex via reentrant projections to these areas (Phelps, 2006; Phelps & LeDoux, 2005; Vuilleumier & Pourtois, 2007), thereby activating sensory cortical processing of emotion. In addition, a magnocellular subcortical pathway subserves the rapid transmission of environmental input from peripheral sensors through the pulvinar thalamus to the amygdala (Leventhal et al., 1985; Schiller & Tehovnik, 2001) to allow for fast threat processing.

However, electrophysiology studies with depth electrodes in the amygdala have reported threat-induced responses well over 100 ms post stimulus (Kreiman et al., 2000; Kuraoka & Nakamura, 2007; Leonard et al., 1985; Oya et al., 2002; Wang et al., 2014), but also see Méndez-Bértolo et al. (2016) for a fast latency of 74 ms. Obviously, such responses are not faster but even slower than activity in the extrastriate cortex as indexed by the P1, let alone the V1 cortical activity as indexed by the C1, implying that the amygdala's reentrant influence is not swift enough to contribute to early threat perception (Adolphs, 2008). Posing further challenge to amygdala dependence in early threat perception, patient SM with complete bilateral amygdala lesions exhibited normal rapid detection and nonconscious perception of fearful faces (Tsuchiya et al., 2009). In addition, a group of 18 participants with unilateral amygdala resections showed intact response to threat in the ventral visual cortex (both ipsilateral and contralateral to the lesion site (Edmiston et al., 2013). Furthermore, two other patients with complete amygdala lesions (Bach et al., 2011) and another group of 26 patients with unilateral amygdala lesions (Piech et al., 2011) displayed comparable enhancement in detecting emotional (vs. neutral) words (relative to healthy controls) in an attentional blink task.

Therefore, extant evidence suggests that early processing of threat could recruit multiple parallel pathways, some of which are located outside the amygdala (Chikazoe et al., 2014; Pessoa & Adolphs, 2010). While the amygdala can modulate later high-level perceptual processing, it may play a relatively small role in initial low-level sensory analysis (Tsuchiya et al., 2009). Challenging the "sensory module" idea, the electrophysiological evidence reviewed earlier raises the possibility that beyond standard sensory analysis, the sensory cortex participates in threat processing, particularly, early threat encoding. Indeed, recent computational modeling of fMRI data support sensory cortical *feedforward input* to the amygdala (instead of the widely assumed amygdala feedback input to the sensory cortex) as an essential mechanism underlying threat processing (Krusemark et al., 2013; Kumar et al., 2012).

## A Sensory Cortical Account of Threat Processing

How does the sensory cortex support threat encoding during initial sensory processing? Using Pavlovian conditioning paradigms, early animal electrophysiological

studies, dated to the 1950s, demonstrated conditioning-related plasticity in the primary and associative auditory cortex (Diamond & Weinberger, 1984; Galambos et al., 1955; Kraus & Disterhoft, 1982; Weinberger et al., 1984). As summarized in excellent reviews (Dunsmoor & Paz, 2015; McGann, 2015; Miskovic & Keil, 2012; Ohl & Scheich, 2005), recent years have witnessed a resurgence of interest in this topic, corroborating and extending the early findings to all sensory modalities in both humans and animals. For instance, a recent fMRI study in our lab demonstrated that newly acquired negative value via aversive conditioning can be represented in the olfactory (piriform) cortex (an associative sensory cortex), which updates the encoding of the conditioned odor, allowing discrimination of this odor from its initially indistinguishable counterpart (Li et al., 2008a).

Animal evidence further suggests that this associative plasticity in the sensory cortex not only emerges immediately after conditioning but also shows long-term retention with growing specificity to the CS (Weinberger, 2004). Importantly, new evidence indicates that this lasting associative plasticity in the associative sensory cortex supports long-term associative emotional memory (Cambiaghi et al., 2016; Grosso et al., 2015a, 2015b, 2016; Kwon et al., 2012). Moreover, this associative sensory cortical plasticity plays a *necessary* role in the long-term retrieval of fear memory (Sacco & Sacchetti, 2010) as sensory cortical efferents to the amygdala activate the basolateral amygdala to trigger fear memory (Cambiaghi et al., 2016). Conceivably, these long-term memory traces can support threat representation in the sensory cortex. Hopefully, this growing body of work would start to dismantle the dichotomy of "sensory module" and "threat module," which has been deeply woven into the fabric of emotion research and theorization. The former, a century-old modularity conceptualization of the sensory cortex, has remained unchallenged to date. Consequently, such efforts will compel sensory cortical accounts of threat processing.

Recently, we have proposed a sensory cortical account of threat processing, which holds that the sensory cortex stores threat codes/representations and independently supports threat encoding as incoming stimuli activate these codes/representations (Li, 2014). As James (1890) asserted, "every perception is an acquired perception"; human perception is largely learned and depends on long-term memory (Goldstone, 1998; Stevenson & Boakes, 2003). Animals and humans are especially adept at developing associative fear learning for biologically prepared objects, sometimes with as few as a single trial (Ohman & Mineka, 2001; Seligman, 1970). In keeping with that, our account takes a learning perspective, building on mnemonically based threat codes/representations acquired through life experiences. Given the associative nature of the olfactory cortex and olfactory perception that is deeply ingrained in associative memory (Gluck & Granger, 1993; Haberly, 1998; Stevenson & Boakes, 2003; Wilson & Stevenson, 2006; Wilson & Sullivan, 2011), we chose olfaction as a model system for this sensory account.

As illustrated in Figure 3.2, this account consists of two key elements: (1) contingency between an odor and an aversive experience induces acquisition/consolidation of aversive associative learning in the amygdala, thereby attaching threat

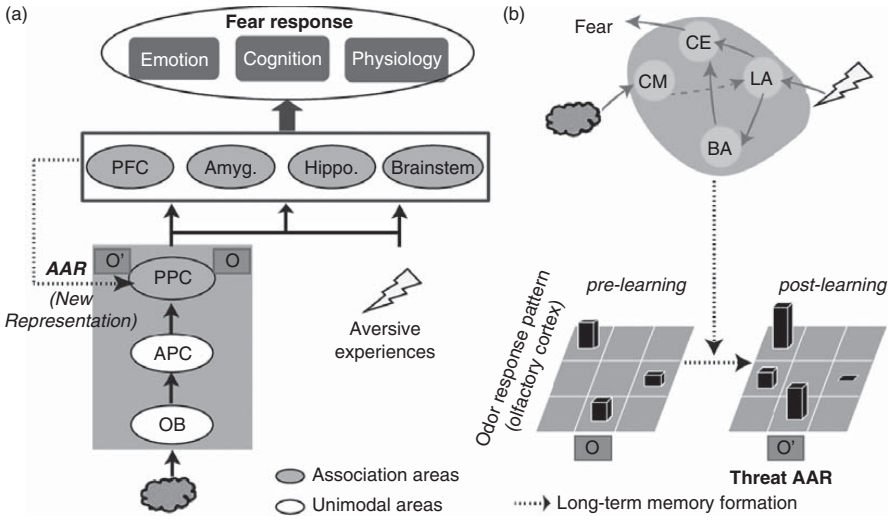


**Figure 3.2** *A sensory cortical model of olfactory threat encoding. (A). Associative learning occurs when an odor is co-experienced with an aversive event. Conditioning-related long-term plasticity results in long-lasting changes in the olfactory (piriform) cortex, updating cortical response pattern to the CS odor. As such, original representation of the odor (O) turns into acquired associative representation/AAR (O'). Such threat AARs constitute the basis of sensory cortical encoding of threat. Later encounters of the same odor will activate O' to directly support threat encoding and trigger emotion responding. (B). Neural mechanisms. Initial association between the odor and aversive experience is formed in the lateral amygdala (LA), which projects directly or indirectly (via the basal nucleus of amygdala/BA) to the central nucleus (CE) to initiate and control fear responses. Over time, the acquired association is converted into a long-term memory trace stored in the piriform cortex supporting the threat AAR. APC = anterior piriform cortex; OB = olfactory bulb; PFC = prefrontal cortex; Amyg. = amygdala; Hippo = hippocampus; CM = corticomedial nucleus of amygdala. Adapted from Li (2014)*

meanings to innocuous odors; and (2) over time, the initial amygdala-based learning gives rise to long-term plasticity in the associative sensory cortex (the piriform cortex), resulting in updated neural response patterns to the conditioned odors. Accordingly, subsequent encounters of these odors will activate the acquired threat representations in the olfactory cortex, supporting olfactory cortical encoding of threat. Finally, outputs from this sensory process (i.e., threat-laden sensory impulses) trigger a constellation of fear responses via projections to a wide range of associative neural networks (especially the amygdala, prefrontal cortex, and brain stem structures).

## A Neurosensory Account of Anxiety

Linking the cognitive model of anxiety (Figure 3.1) and the sensory cortical model (Figure 3.2) of threat processing, here we propose a neurosensory model of anxiety

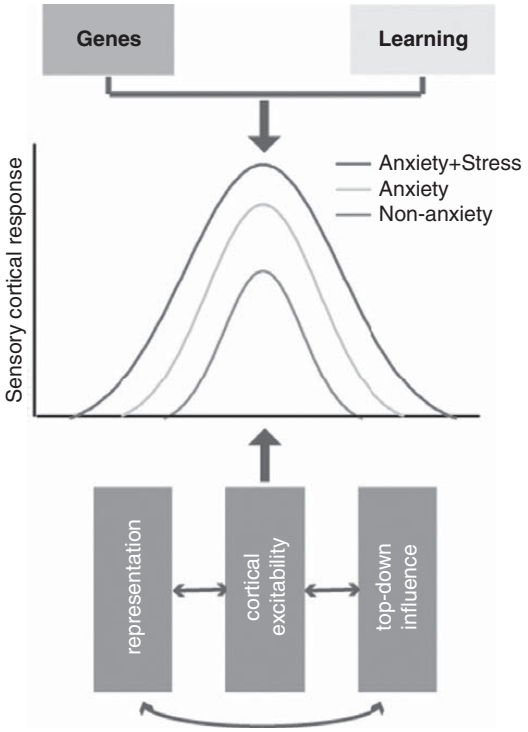


**Figure 3.3** *A neurosensory model of anxiety. The three curves represent sensory cortical activity in individuals with low anxiety, high anxiety, and high anxiety and high stress (e.g., stressful, anxiety-provoking contexts, chronic or acute life stress), respectively. The three boxes in the bottom refer to the three key mechanisms underlying sensory cortical hyperactivity, which often interact with each other to generate synergistic effects.*

(Figure 3.3). We propose that three mechanisms can underlie enhanced sensory cortical response to threat in anxiety, which, in turn, feeds into the second and third stages of threat processing (i.e., the primal mode and the metacognitive mode), triggering a cascade of threat responses to induce and perpetuate anxiety. Specifically, consequent to a combination of genetic predispositions and negative environmental exposures and experiences (i.e., aversive learning), three pathological processes emerge in sensory cortical encoding of threat among anxious individuals: (1) intensified activation of threat representation, which consequently tunes up sensory cortical sensitivity and responsivity to threat stimuli; (2) broad enhancement in sensory cortical excitability, resulting in broad sensory hypersensitivity and hyper-responsivity to all incoming stimuli; and (3) biased top-down influence in favor of threat-related predictive coding of upcoming stimuli. Importantly, these three mechanisms can interact with each other to generate synergistic effects.

Concerning the first mechanism, animal electrophysiological data of associative learning via Pavlovian conditioning have revealed preferential sensory tuning of the conditioned stimuli (CS) (Weinberger, 2007). Conditioning can shift the sensory cortical turning curve to optimally respond to the CS. For example, a neuron in the A1 (primary auditory cortex) of the guinea pig shifted its preconditioning best frequency of 0.75 KHz to the CS frequency of 2.5 KHz after tone-shock conditioning (Bakin & Weinberger, 1990). Conditioning can also expand the receptive field of the CS such that more neurons become responsive to the CS cue. Both CS-specific tuning shifts and CS-specific receptive field enlargement can heighten the activation of threat representation in the sensory cortex such that only minimal sensory input is required to activate threat response. Although such low-level tuning plasticity remains difficult to assess in humans, these animal findings provide useful explanations for the heightened threat response in early sensory processing, which could be especially exaggerated in anxiety.

In line with the second mechanism, besides this threat-specific sensory hyperactivity, many studies reviewed earlier show that anxious individuals display a broad enhancement in early sensory processing, regardless of the emotional content of the stimuli. In that section, we alluded to a possible explanation of hypervigilance, which is general, threat-neutral exaggeration of basic sensory processing. This means that in order to maintain a high level of alertness to readily detect environmental threat, the sensory cortex in anxious individuals would have adapted to a high level of excitability such that it can be activated with minimal sensory input. Such broad sensory cortical excitability is highly susceptible to fluctuations in levels of brain monoamines, including norepinephrine, dopamine, and serotonin (Hurley et al., 2004). It is known that anxiety can lead to chronic, tonic increases of noradrenergic and dopaminergic levels, which would result in suppressed sensory gating and heightened postsynaptic activity in the sensory cortex (i.e., increased sensory cortical excitability) (Adler et al., 1988; Aston-Jones et al., 1994; Baisley et al., 2012; Berridge & Waterhouse, 2003; Sherin & Nemeroff, 2011; Southwick et al., 1997).

In an fMRI study, we induced an anxious state in participants and examined their basic olfactory cortical responses to neutral odors before and after anxiety induction (Krusemark et al., 2013). Our data indicate significant increases in information relay from the low-level, primary to a higher-level (associative) olfactory cortex as a result of induced anxiety, highlighting decreased sensory gating in anxiety (Figure 3.4A). Importantly, paralleling this neural change, participants perceived the initially neutral odors as somewhat negative post anxiety induction, suggesting that anxiety-related sensory gating reduction can contribute to biased threat perception. In keeping with these findings, an early ERP study using a standard paired-click paradigm demonstrated a lack of repetition suppression such that the P1 potential failed to show a dampened response to the second click, suggesting reduced sensory gating in patients with PTSD (Skinner et al., 1999).

A new study from our lab further revealed that even during an idling state with no sensory stimulation (also known as a resting state), patients with PTSD exhibited

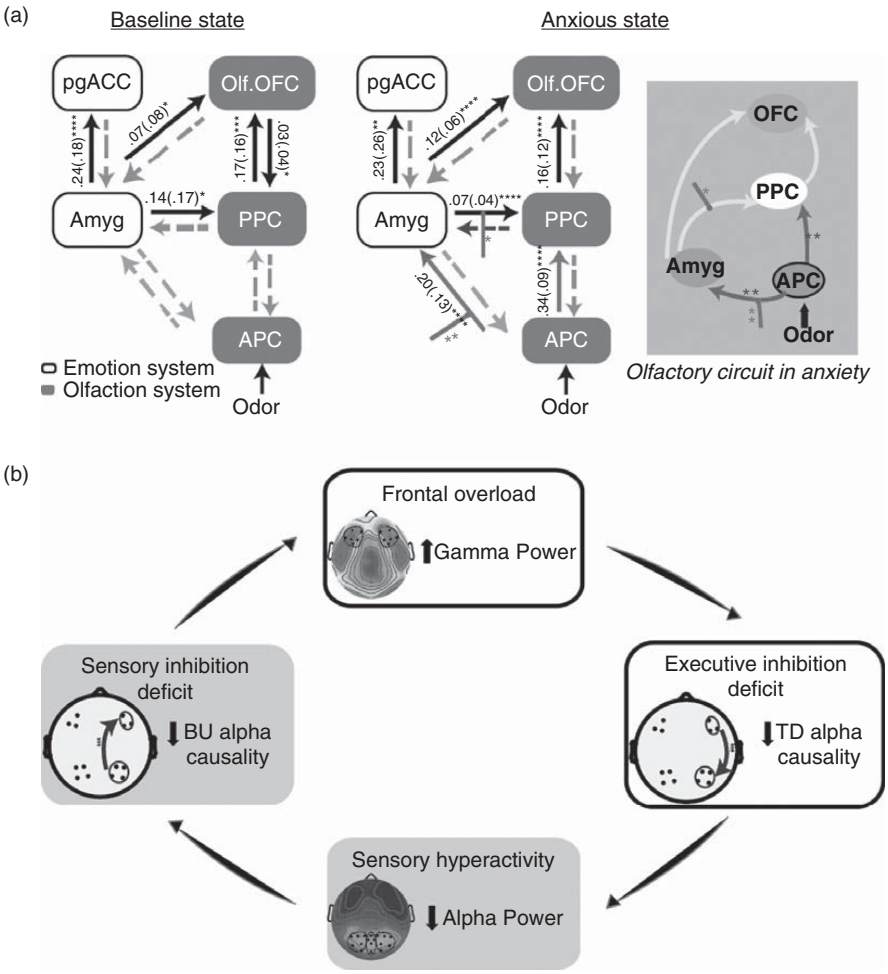


**Figure 3.4** *Deficient sensory gating in anxiety. (A). The olfactory sensory pathway adapts readily with induced anxiety, characterized by strengthened APC efferents to the amygdala and PPC and amplified amygdala efferents to the PPC. This olfactory circuitry reorganization is accompanied by a significant negative shift in perceived pleasantness of odors (not shown here). Yellow lines represent intrinsic connections initially significant, green lines those that become significant in anxiety, and red intercepting lines modulation by odors in anxiety. (B). A vicious cycle in PTSD, rooted in sensory hyperactivity at resting: (1) sensory hyperactivity, (2) deficient bottom-up (BU) sensory inhibition, (3) frontal overload (due to sensory overflow), and (4) deficient top-down (TD), executive inhibition and regulation. OFC = orbitofrontal cortex; PPC = posterior piriform cortex; pgACC = pregenual anterior cingulate cortex; Amyg. = amygdala; olf. = olfactory; APC = anterior piriform cortex. Panel A adapted from Krusemark et al., 2013, and Panel B from Clancy et al., 2017.*

markedly suppressed alpha oscillatory activity in the visual cortex (Clancy et al., 2017). Alpha oscillations represent a primary mechanism of sensory gating, with greater alpha power associated with greater sensory gating and lower sensory cortical excitability (Bollimunta et al., 2008; Foxe & Snyder, 2011; Klimesch, 2012; Palva & Palva, 2007; Shaw, 2003; Worden et al., 2000). The severely depressed alpha activity in patients with PTSD, during a resting state, underscores the severity of sensory hyperactivity such that the sensory cortex remains active even in the absence of any sensory input. Accompanying this alpha deficit, patients with PTSD also exhibited deficient bottom-up inhibitory influence along with heighted frontal gamma activity. These aberrations together form a vicious cycle in PTSD that is in action even at rest, where intrinsic sensory hyperactivity and disinhibition give rise to frontal overload and disrupt executive control, fueling and perpetuating PTSD symptoms (Figure 3.4B).

Notably, absent in generalized anxiety disorder, these aberrations highlight a unique sensory pathology of PTSD (ruling out effects of mere anxious hyperarousal), suggesting that in extremely severe anxious conditions, sensory hyperactivity can be constant and pervasive. In fact, such broad sensory anomalies in PTSD draw an interesting parallel to more severe mental illnesses such as psychosis, where sensory anomalies have been recognized as part of the pathology (Geyer et al., 2001; Park et al., 2015; Thoma et al., 2003). Such broad sensory hyperactivity and gating deficits would allow irrelevant sensory input to inundate the entire information-processing stream, proliferating brain-wide dysfunctions and causing significant cognitive and executive dysfunctions (Javitt, 2009).

Concerning the third mechanism, the "New Look" movement in the middle of the past century made a strong argument for higher-order cognitive processes (prediction, expectation) and motivation to influence perception (Bruner, 1957; Bruner et al., 1951). This concept fits Beck's cognitive schema model in that information processing is performed according to a person's view of the world and the self (Beck, 1967), and has inspired emotion theorists to promote the idea of "seeing it with feelings" (Barrett & Bar, 2009), namely, standard object perception being influenced by affective predictions. The "New Look" theory has received a resurgence of interest in the past few years, owing to recent discoveries in cognitive and computational neuroscience (Clark, 2013; Friston, 2012). Simply put, this view holds that the brain regularly generates predictions about an upcoming stimulus based on prior knowledge. In keeping with that, multiple groups have observed that expectation and prediction shifts responses in both visual (Kastner et al., 1999; Puri et al., 2009; Stokes et al., 2009) and olfactory (Zelano et al., 2011) cortices to otherwise invariant visual or olfactory stimuli.

Anxiety has long been characterized by heightened prediction and anticipation of negative future events. For instance, anxious individuals tend to overestimate the probability and cost of negative events (Butler & Mathews, 1983; Grupe & Nitschke, 2013; Mitte, 2007). Conceivably, this negative world view would bias their prediction of upcoming events negatively. By this token, the sensory cortex of anxious individuals would receive threat-laden, top-down input (from the

prefrontal cortex) before stimulus onset such that sensory cortical activity will prioritize threat encoding and impede neutral encoding.

In sum, we propose three mechanisms that can be at play synergistically in the sensory cortex to facilitate sensory threat processing. Current neural models of anxiety and related disorders have concentrated on the prefrontal-cortex-amygdala circuit pathology in response to threat; namely, anxiety disorders are associated with hypoactivity in the ventromedial prefrontal and anterior cingulate cortices (especially in PTSD) and hyperactivity in the amygdala in response to threat (Etkin & Wager, 2007; Patel et al., 2012; Rauch et al., 2006; Shin & Liberzon, 2010). The inclusion of these sensory mechanisms would expand our conceptualization of anxiety pathophysiology to a tripartite sensory-prefrontal-cortex-amygdala circuit that has gone awry in anxiety. Manifested in information processing, the tripartite neural circuit pathology in anxiety can exaggerate sensory cortical threat "tagging" and intensify subsequent processes such as attention and interpretation. Furthermore, these sensory mechanisms are likely to interact with downstream mechanisms such as selective attention to threat and negative interpretations, engendering compounded, supra-additive impacts on information processing to underpin a host of anxiety-related symptoms. Last but most important, the identification of attentional and interpretational biases in anxiety has motivated new anxiety treatments using inventive protocols to rectify these biases. We hope that the knowledge of sensory mechanisms underlying anxiety pathology can encourage more research in this area and, more important, inspire novel interventions targeting sensory processing and the sensory brain in anxious patients.

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