

# Neural substrates of cognitive bias and anxiogenesis

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## Abstract

This review is designed to provide a brief overview of biology of stress-induced neurocognitive processing and mechanisms that contribute to susceptibility (reactivity) and resistance (resiliency) to anxiogenic disorders and examine a potential for developing experimental paradigm better suited for identifying new treatment targets.

## Introduction

Processing of stressful stimuli and periodically feeling somewhat anxious is an aspect of animal and human development [1], however the increasing global prevalence of anxiety disorders is compelling investigations focused primarily on when and how these feelings become clinically significant disorders. The abundance of published scientific literature indicates the efforts devoted to understand the biology of neurocognitive processing of stressful stimuli and the pathophysiology associated with these processes. Although these efforts have produced therapeutically useful pharmacologic treatment strategies, the abuse potential and side effects of these agents, their limited usefulness in pediatric and elderly population, and women [2] combined with increasing global burden of anxiety-related disorders [3,4] is driving the search for better treatment strategies for these disorders. Varying definitions and techniques of inducing stress, difficulties in connecting animal and human behavior to specific neuronal pathway and the nature of evolving diagnostic criteria present additional challenges. Use of clearly defined criteria for testing and characterizing anxiety and depression-related behaviors in animal models have also been proposed [5].

Anxiety has been described as an innate behavioral response necessary for survival and adaptation to the environment and clinicians define it as “a subjective sense of unease, dread, or foreboding, and can indicate a primary psychiatric condition or its component” [6]. Disorders with pathologies that include anxiety-related debilitating psychological and physiologic responses are widespread in the U.S. and according to one report about 18% of adults may seek treatment for anxiety disorder [7]. A recent study analyzed global burden and regional occurrence of anxiety disorders and estimated that the prevalence of anxiety disorders was 7.3% and ranged from 5.3% in African cultures to 10.4% in Euro/Anglo cultures [3,4]. Continuous presence of images of natural and man-made disasters including presence of terrorist atrocities on widely circulated digital media has added to the sources of potentially anxiogenic stimuli and it has been suggested that global burden of anxiety disorders will increase significantly [1,8].

Thus, biology of effects of stress has been a focus of several studies and it has been fairly well established that distinct brain regions are involved in processing stress stimuli and generating adaptive responses as a part of animal and human survival, and that defects in these processes can lead to anxiety disorders [9-11]. However, a conundrum

in these efforts is that while much of the research in animal models has focused on adaptive responses to threat stimuli that activate mechanisms in acquisition and extinction of fear [12-14], human anxiety disorders are related to defects in processing less ambiguous stimuli associated with uncertainty of threat [13-17] and cognitive bias is a key component of the pathogenesis of human anxiety disorders [1]. Thus, while significant progress has been made towards understanding the biological processes in fear conditioning and extinction, biological basis of neurocognitive processing of ambiguous worry some stimuli related to human anxiety disorders is not as clearly understood.

## Cognitive processing of stressful sensory input

Mechanisms involved in processing information regarding stress/threat have been reviewed extensively [1,18-20]. A conceptual overview of the cognitive processing of stress stimuli in anxiety disorders is depicted in Figure 1. It has been proposed that negative cognitive biases play a central role in the onset and maintenance of anxiety and depression [21-25]. The downstream effects of these biases such as negative self-evaluation, heightened arousal, and increased anxiety have also been demonstrated [26,27]. A cognitive processing model of fear and anxiety, linking distinct brain structures to specific stages of information processing of perceived threat has also been proposed [28]. These studies have led to the proposition that the human anxiety disorders can be divided in two categories: Those characterized by an underactivity of the prefrontal cortex, disinhibition of amygdala and intense fear and panic (Panic disorder, post-traumatic stress disorder, and phobias); and disorders that involve worry and rumination are characterized by an over activity of the prefrontal cortex (Generalized Anxiety Disorder and Obsessive-Compulsive Disorder) [29].

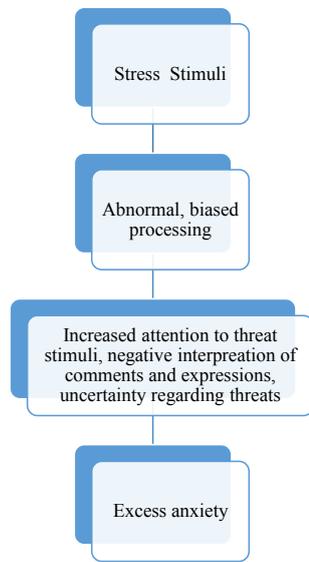
## Amygdala reactivity and anxiety disorders

Many studies have established that early life experiences affect the manner in which amygdala reacts to stress later in life. A long-

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**Figure 1.** Overview of cognitive processing of stress stimuli in anxiety disorders (based on references cited in the text).

standing hypothesis that exposure to adverse environment during sensitive developmental phases is a risk factor for the development of mental disorders [30] has received considerable support by several studies carried out since then [11,31,32]. Briefly, these studies indicate that harsh environment generates stronger amygdala responses and individuals exposed to these environments are unable to recruit the prefrontal cortex effectively for regulating emotional responses to threatening cues [33]. Increased anxiety-related temperamental traits in young adults was found to be associated with increased amygdala and insula reactivity to certain types of emotional processing in social anxiety [34] and posttraumatic stress disorder (PTSD) [35].

Thus, amygdala reactivity to anxiogenic stimuli appears to be central in the pathogenesis of anxiety disorders and many studies indicate that it is affected by a variety of factors [36-42]. These studies indicate that 5-HTTLPR (serotonin-transporter-linked polymorphic region) may be a susceptibility factor for affective disorders by biasing the functional reactivity of the human amygdala when challenged with stress and/or deficient cortical regulatory input [38]. A functional variation in the human 5-HT1A gene [39,40], polymorphism in the androgen receptor gene [41], and regulatory variant of human tryptophan hydroxylase-2 gene [42] have also been observed to bias the reactivity of the amygdala. Recently role of sleep quality on the relationships between amygdala reactivity and perceived stress among men has also been examined [36].

### HPA and resiliency

Similarly, investigations have also been focused on those mechanisms that may prevent or minimize the risk of triggering pathogenic changes leading to anxiety [43]. It has been proposed that processing of sensory data induce physiological changes (allostatic changes) that result in adaptive responses to maintain the homeostasis, and that the intensity and duration of these changes (allostatic overload or load) may trigger the onset of anxiogenic pathophysiology [44]. Using allostatic changes and allostatic load as a conceptual framework,

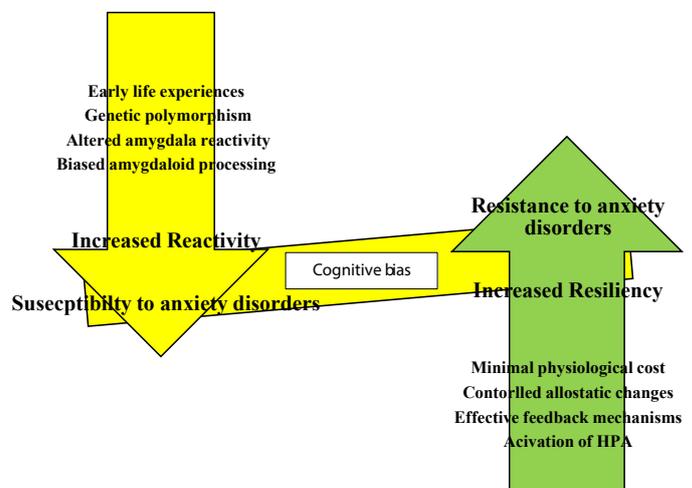
efforts have been made to examine how the allostatic changes turn into allostatic load and what pharmacological manipulations may minimize the risk of allostatic changes becoming the allostatic load (resiliency). Role of hypothalamic-pituitary axis (HPA) in processing of stress-induced responses has been examined extensively, particularly as a potential targets for developing resiliency. The feedback mechanisms in the HPA regulate the intensity and duration of HPA activation in response to acute stress and are particularly important since they may contribute to the conversion of allostatic changes into allostatic load leading to psychopathology [43]. An overview of effects of reactivity and resilience on cognitive balance is shown in Figure 2.

### Animal models

For research in animal models, a validity-based approach for testing role of various mechanisms that contribute to cognitive bias and the underlying biology. The proposed criteria for validation of animal models for anxiety and depression studies [5] define a paradigm better suited for this type of focused research. By providing face validity, predictive validity, and construct validity, this paradigm has a potential to better connect the studies of cognitive bias with those focused on susceptibility or resilience. Development and use of endophenotypes for cognitive bias may also add to the progress made in this area. Anxiety endophenotypes such as impaired fear extinction and fear generalization for post-traumatic shock disorder [45], elevated startle response for general anxiety disorder [46], and increased blood oxygenation level dependent (BOLD) amygdala response to threat for panic disorders [47] offer opportunities to investigate the connectivity between cognitive bias and susceptibility of mechanisms mediated by amygdala and HPA further.

### Conclusion

Thus, there is sufficient evidence in the literature to support role of cognitive processing of stressful stimuli in amygdala and generation of adaptive responses mediated by the HPA in angiogenesis and susceptibility of these mechanisms to anxiogenic factors. A closer examination of these processes for their susceptibility to anxiogenic pathology may provide additional strategies for treatment of anxiety disorders.



**Figure 2.** A conceptual overview of effects of reactivity (shown with the yellow arrow) and resilience (shown with the green arrow) on cognitive bias.

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