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Exaggerated neurobiological sensitivity to threat as a mechanism linking anxiety with increased risk for diseases of aging

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Abstract

Anxiety disorders increase risk for the early development of several diseases of aging. Elevated inflammation, a common risk factor across diseases of aging, may play a key role in the relationship between anxiety and physical disease. However, the neurobiological mechanisms linking anxiety with elevated inflammation remain unclear. In this review, we present a neurobiological model of the mechanisms by which anxiety promotes inflammation. Specifically we propose that exaggerated neurobiological sensitivity to threat in anxious individuals may lead to sustained threat perception, which is accompanied by prolonged activation of threat-related neural circuitry and threat-responsive biological systems including the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), and inflammatory response. Over time, this pattern of responding can promote chronic inflammation through structural and functional brain changes, altered sensitivity of immune cell receptors, dysregulation of the HPA axis and ANS, and accelerated cellular aging. Chronic inflammation, in turn, increases risk for diseases of aging. Exaggerated neurobiological sensitivity to threat may thus be a treatment target for reducing disease risk in anxious individuals.

Keywords

Anxiety; Attentional bias; Cellular aging; Diseases of aging; Hypothalamic-pituitary-adrenal axis; Inflammation; Information processing; Neurobiological; Parasympathetic nervous system; Psychoneuroimmunology; Sympathetic nervous system; Threat

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Still, thou art blest, compar'd wi' me!

The present only toucheth thee:

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But Och! I backward cast my e'e,

On prospects drear!

An' forward, tho' I canna see,

I guess an' fear!

"To A Mouse" by Robert Burns

Being anxious throughout life has implications not just for subjective wellbeing, but also for physical health and longevity. This is because individuals who experience chronically high levels of anxiety are at increased risk for several diseases of aging, including cardiovascular, autoimmune, and neurodegenerative diseases, as well as for early mortality (Benninghoven et al., 2006; Carroll et al., 2009; Eaker et al., 2005; Kubzansky and Kawachi, 2000; Li et al., 2008; Martens et al., 2010; Roy-Byrne et al., 2008; Spitzer et al., 2009). Given that anxiety disorders have the highest lifetime prevalence of any psychiatric disorder, affecting up to 30% of the population over the lifespan, these findings highlight a highly prevalent and modifiable risk factor for physical disease (Demyttenaere et al., 2004; Kessler et al., 2005). Nonetheless, when compared with other major psychiatric disorders like depression, relatively little attention has been paid to examining the role anxiety plays in promoting and exacerbating physical disease. Moreover, little clinical consideration is given to addressing the physical health consequences of anxiety. This lack of attention is striking given that anxiety may be an even stronger risk factor for physical illness than depression (Kubzansky and Kawachi, 2000).

Despite strong evidence that anxiety negatively impacts physical health, the mechanisms that underlie these effects remain poorly understood. Previous research confirms that various forms of anxiety – including trait anxiety, state anxiety, and clinical anxiety disorders – are associated with elevated inflammation (Carroll et al., 2011; Hoge et al., 2009; O'Donovan et al., 2010; Pitsavos et al., 2006). In turn, elevated inflammation is a strong and robust risk factor for several diseases of aging including cardiovascular, autoimmune, and neurodegenerative disorders (Akiyama et al., 2000; Bruunsgaard et al., 2001; Freund et al., 2010; O'Donovan et al., 2011b; Ridker et al., 2000). However, an integrative model of the cognitive-behavioral and neurobiological mechanisms linking anxiety and inflammation has been lacking.

In the present paper, we address this gap in the literature by proposing a neurobiological model of the mechanisms by which anxiety may increase risk for diseases of aging. In this model, exaggerated neurobiological sensitivity to threat is proposed as a common feature across multiple anxiety disorders that plays a key role in the relationship between anxiety and inflammation. To introduce this model, we first outline differences and commonalities among the anxiety disorders. Then, we introduce evidence that diverse anxiety disorders are characterized by exaggerated neurobiological sensitivity to threat, as indexed by cognitive biases in threat-related information processing, and abnormalities in central and peripheral neurobiological systems involved in threat perception. We then explore the consequences of such neurobiological responding for inflammation, and present evidence for the role of chronic inflammation in promoting the development and progression of diseases of aging

that have earlier onset and greater prevalence in anxious individuals. Finally, we bring these ideas together in a single integrative model, and discuss the clinical and public health implications of this work, as well as several avenues for future research.

1. Anxiety disorders and diseases of aging

Anxiety disorders, the most prevalent neuropsychiatric disorders worldwide, include generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), social anxiety disorder, panic disorder, obsessive-compulsive disorder (OCD), agoraphobia, and specific phobia (Kessler et al., 2005). Although these disorders are phenotypically diverse with symptoms ranging from enduring worry in GAD, to hypervigilance in PTSD, to compulsive hand washing in OCD, they also have common genetic, cognitive-behavioral, and biological features (Enoch et al., 2008; Lara et al., 2006; Zhou et al., 2008). One shared biological feature is elevated inflammation (Brennan et al., 2009; Gill et al., 2009; Hoge et al., 2009; O'Donovan et al., 2010; Pace and Heim, 2011; Von Kanel et al., 2010), which in turn is associated with accelerated biological aging and increased risk for the development of a variety of chronic diseases (Akiyama et al., 2000; Freund et al., 2010; Koenig et al., 2008; O'Donovan et al., 2011b; Ridker and Morrow, 2003; Ridker et al., 2002). Although inflammation may contribute to elevated disease risk in anxious individuals, it is not clear how having an anxiety disorder confers increased risk for elevated inflammation.

One possibility is that anxious individuals have elevated inflammation because of a greater tendency to smoke, eat poorly, be physically inactive, and abuse substances such as alcohol and drugs (Azevedo Da Silva et al., 2012; Schneider et al., 2010; Strine et al., 2005; Wolitzky-Taylor et al., 2012). However, not all anxious individuals exhibit poor health behaviors (Eifert et al., 1996), and most (Hoge et al., 2009; Pitsavos et al., 2006; von Kanel et al., 2007) but not all (Copeland et al., 2012) studies of the relationship between anxiety disorders and inflammation indicate that the association is independent of such factors. Another possibility is that neurobiological abnormalities associated with anxiety disorders promote inflammation. Exaggerated neurobiological sensitivity to threat, a common abnormality across diverse anxiety disorders, may increase risk for repeated and prolonged activation of biological stress systems, including inflammatory systems. When sustained, as in the case of a chronically anxious individual, such activation could drive functional and structural biological changes that promote chronic inflammation. Thus, exaggerated neurobiological sensitivity to threat may play a key role in the relationship between anxiety and inflammation.

2. Neurobiological sensitivity to threat

The ability to perceive and respond to environmental threats is fundamental to survival; without it, our ancestors would have died young and failed to pass on their genes. Given this strong selective pressure, it is not surprising that human threat perception and response systems comprise an exquisitely coordinated network that extends across central and peripheral bodily systems and is programmed to respond proactively to protect against injury and infection (Stein and Nesse, 2011; Woody and Szechtman, 2011). To facilitate survival, humans maintain vigilance for threatening information and are able to quickly

mount appropriate biological and behavioral responses to threat. This vigilance and preparedness is costly, though, and can interfere with the pursuit of other goals such as reward seeking and bodily repair. Thus, threat perception and response systems must be tightly regulated and appropriately calibrated to the environment (Blanchard et al., 2011). Negative emotions may play a key role in the calibration of this system, insofar as they promote vigilance for threatening information and readiness to confront or avoid threats (Dolan, 2002). Although emotional enhancement of threat-related information processing confers obvious advantages in dangerous environments, it is biologically costly and needs to be switched off when no longer appropriate. That is, threat-related vigilance and preparedness must be up-regulated when physical or social threats are likely (e.g., in a warzone) and down-regulated when such threats are unlikely (e.g., in one's own home).

2.1. Anxiety and exaggerated neurobiological sensitivity to threat

Anxiety disorders represent one context in which emotional enhancement of threat-related information processing is maladaptive, leading to exaggerated threat sensitivity. Unlike fear, which is a generally adaptive short-lived state of apprehension related to a proximal threat, anxiety is a sustained emotion aroused by distal and diffuse threats (Davis et al., 2009; Grillon, 2008). Thus, anxiety-related enhancement of threat-related information processing can persist across time and have chronic effects. A large body of literature and numerous excellent reviews document the complexities of enhanced threat-related information processing in anxious individuals (Britton et al., 2011; Cisler and Koster, 2010; Stein and Nesse, 2011), and here we provide a broad overview.

In the earliest stages of threat-related information processing, anxious individuals detect threatening stimuli (e.g., angry faces or predatory animals) more quickly than non-anxious individuals (Bar-Haim et al., 2007; El Khoury-Malhame et al., 2011; MacLeod et al., 1986). In the subsequent appraisal stage, anxious individuals are likely to regard ambiguous and threatening stimuli (e.g., mild electric shocks in the laboratory and motor vehicle accidents in real life) as more threatening than they actually are (Boddez et al., 2012; Britton et al., 2011; Dash and Davey, 2012; Lazarus and Folkman, 1984; Meiser-Stedman et al., 2009). This may contribute to the tendency for anxious individuals to show greater neurobiological reactivity to standardized threatening stimuli such as a virtual audience for a public speaking task or angry and fearful human faces (Cornwell et al., 2011; Eldar et al., 2011; Robinson et al., 2012a). Finally, following such reactions, anxious individuals engage in cognitive-behavioral avoidance of perceived threats, which limits their ability to challenge inappropriate threat perception, confront and resolve threatening situations, and reshape expectations for the future (Cisler and Koster, 2010; Koster et al., 2006).

Even worry, a symptom of anxiety that may superficially resemble an attempt to engage with perceived threats, has been conceptualized as a form of cognitive avoidance that facilitates evasion of threatening imagery and inhibition of emotion processing (Borkovec and Hu, 1990; Borkovec and Inz, 1990). For example, worry can facilitate avoidance of a distressing mental image (e.g., of oneself being humiliated in front of a large audience) by allowing the attention to be directed away from the image and towards abstract thoughts related to the situation (e.g., "I am a failure"). Evidence for this avoidance function of worry

is found in studies demonstrating that worry is associated with enhanced distraction from other emotionally distressing images and reduced physiological reactivity to subsequently encountered threats (Borkovec et al., 1993; Borkovec and Roemer, 1995; Llera and Newman, 2010). Ultimately, however, the avoidance function of worry is only partially fulfilled, because worry in itself leads to sustained emotional distress and prolonged physiological arousal (e.g., Newman and Llera, 2011). The ultimate result of this process is failure to achieve resolution of perceived threats, resulting in sustained threat perception. We illustrate these dynamics in Fig. 1, which depicts a model of threat-related information processing in anxious and non-anxious individuals.

Support for the existence of biases in threat-related information processing in anxious individuals is particularly strong in the context of clinical anxiety disorders. In fact, several theoretical models implicate threat-related attentional biases in both the development and maintenance of anxiety disorders including GAD, PTSD, social anxiety disorder, panic disorder, OCD, and simple phobia (Beck, 1985; Beck et al., 1985; Dalgleish et al., 2003; MacLeod and McLaughlin, 1995; Mathews et al., 1990, 1989; Taghavi et al., 2003). Despite the diverse clinical presentations of individuals with different anxiety disorders, a meta-analytic review indicated that the magnitude or severity of the threat-related attentional bias is not significantly different between these disorders (Bar-Haim et al., 2007) and cognitive-behavioral avoidance is also a core feature of all anxiety disorders (APA, 2000). In fact, the most successful psychotherapeutic treatments for anxiety disorders are cognitive-behavior therapy and prolonged exposure, both of which involve progressively exposing anxious individuals to stimuli perceived as increasingly threatening in order to break the cycle of vigilance and avoidance (Beck, 1976; Beck et al., 1985; Foa and Kozak, 1986). When such treatments are ineffective, or when they are not applied, anxious individuals tend to experience sustained threat perception, which leads to emotional distress and impaired quality of life (Beck et al., 1985; Cisler and Koster, 2010; Stein and Nesse, 2011). Moreover, such biases in threat-related information processing may promote neurobiological processes that increase disease risk. Below, we outline the neural underpinnings of threat-related information processing and the potentially deleterious consequences of threat perception for neuroendocrine, autonomic, and inflammatory systems.

3. Neurobiology of threat sensitivity

3.1. Neural processing of threatening information

The neural substrates that subserve threat-related information processing have been studied extensively in animal models and in humans. In humans, this has been done by exposing individuals to a wide range of stimuli including angry and fearful faces, dangerous scenes, threatening words, distressing memories, and phylogenetic threats such as snakes and spiders (Bishop, 2007, 2008; Woody and Szechtman, 2011). Although the specific sites of neural activation differ somewhat across these stimuli, several brain regions have emerged as being engaged in response to stimuli perceived as threatening. These regions include the amygdala, hippocampus, medial prefrontal cortex (mPFC), bed nucleus of the stria terminalus (BNST), and periaqueductal gray (PAG) (Davis et al., 2009). Coordinated engagement of these regions is critical for detecting threats, and for regulating behavioral

and biological responses to threat. Importantly, however, activity in this threat-related neural network is potentiated for individuals with anxiety disorders, as well as for persons exhibiting high levels of trait anxiety (Bishop, 2007, 2008).

One particularly important brain region for threat-related information processing is the amygdala (Bishop, 2008; Davis and Whalen, 2001; LeDoux, 2000). The amygdala is a limbic brain structure that has been described as a "neural watchdog" insofar as it responds quickly – even before conscious awareness – to possible threats in the environment (Anderson et al., 2003; Whalen et al., 2004). The amygdala responds to both positive and negative stimuli (Hennenlotter et al., 2005; Somerville et al., 2004), and thus plays a key role in determining the extent to which environments are perceived as safe versus dangerous (Tottenham and Sheridan, 2010). The amygdala is particularly responsive to cues representing danger or threat, such as emotional faces and masked fearful whites of human eyes (Cunningham et al., 2008; Davis and Whalen, 2001; Whalen et al., 2004). Amygdalar responses are tightly calibrated under normal circumstances, but are exaggerated in the context of anxiety disorders (Rauch et al., 2000; Stein and Nesse, 2011). In fact, greater amygdala responses to threat, as measured by functional imaging paradigms involving exposure to threatening stimuli such as emotional faces, is positively correlated with the severity of anxiety symptoms (Armony et al., 2005; Fredrikson and Furmark,2003; Phan et al., 2006; Protopopescu et al., 2005). Neural activity in the amygdala has also been found to mediate symptoms related to anxiety, such as PTSD-related hyperarousal (Rauch et al., 2003).

The amygdala does not function in isolation but rather in concert with other brain regions that regulate its activity, such as the hippocampus and mPFC, which have extensive connections to the amygdala (Bishop, 2007, 2008). The hippocampus is involved in learning and episodic memory, and is critical for explicit encoding of threat-related contextual cues (Bishop, 2007; Phelps, 2004; Shin et al., 2006). Patients with hippocampal damage, for example, are physiologically aroused by neutral stimuli that have been paired with shock but are unable to explicitly recollect that the stimuli and shock were ever associated with each another (Bechara et al., 1995). Moreover, the hippocampus stores information that gives the amygdala the ability to respond to environmental threats that a person has been told about, but never directly experienced (e.g., a dangerous predator or neighborhood), enabling individuals to experience anticipatory anxiety for symbolic or imagined situations, a key process in anxiety disorders (Phelps et al., 2001).

The mPFC, on the other hand, is involved in fear extinction learning, or the acquired down-regulation of threat-related responses after threats have passed (Milad and Quirk, 2002; Milad et al., 2006). This mechanism for down-regulating cued and contextual fear is impaired in anxious individuals, resulting in sustained physiological symptoms of anxiety (Indovina et al., 2011). It has been proposed, therefore, that the maintenance of anxiety stems from exaggerated amygdala responsivity to threat resulting from a lack of adequate regulation of amygdala activity by the mPFC (Bishop, 2007; Indovina et al., 2011).

The amygdala, hippocampus, and mPFC function as components of an integrated network involved in detecting and monitoring potential threats, and regulating behavioral and

biological responses to such threats (Bishop, 2007; Indovina et al., 2011; Rauch et al., 2003; Shin et al., 2006). Other brain structures in this network include the BNST and the PAG. The BNST is involved in monitoring the proximity of threat and in coordinating autonomic and motor responses to threat (Davis et al., 2009; Davis and Whalen, 2001; Mobbs et al., 2007; Somerville et al., 2010; Walker et al., 2003), and the PAG is involved in activating stereotyped defensive reactions to threat, such as immobility and panic, which are engaged during periods of intense fear or imminent threat (Mobbs et al., 2007; Nashold et al., 1969). Finally, a large number of neuroimaging studies have examined the brain regions that are engaged during exposure to social threats, such as social exclusion or rejection, which signal an increased likelihood of possible physical threat. Brain regions engaged during these experiences include the dorsal anterior cingulate cortex (dACC) and bilateral anterior insula, which are key nodes in the neural pain network (Eisenberger et al., 2003; Kross et al., 2011; Slavich et al., 2010b). Fig. 2 illustrates some of the key reciprocal connections within the neural network involved in threat-related information processing.

3.2. Neurobiological responses to threat perception

The brain regions involved in processing threatening information can activate biological stress-response systems, including the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) (Dickerson and Kemeny, 2004; Mendes et al., 2007; Seery, 2011; Thayer et al., 2012). In the case of the HPA axis, cortical and subcortical brain regions involved in threat-related information processing have direct projections to neurons in the paraventricular nucleus of the hypothalamus, which signals downstream via the pituitary release of ACTH to promote the secretion of the glucocorticoid hormone cortisol from the adrenal cortex (An et al., 1998; Ongür et al., 1998). Numerous experimental studies have shown increases in cortisol in response to social-evaluative threat (Epel et al., 2000; Gruenewald et al., 2006; Taylor et al., 2008). Moreover, in a meta-analytic review of 208 studies, threat emerged as one of the key features of psychological stressors that elicit increases in cortisol (Dickerson and Kemeny, 2004).

The brain regions involved in threat-related information processing also regulate the ANS, and activity in the amygdala strongly correlates with activity in both the sympathetic and parasympathetic branches of the ANS (An et al., 1998; Critchley, 2005, 2009; Ongür et al., 1998; Salomé et al., 2007; Thayer et al., 2012; Tsukiyama et al., 2011). The mPFC can influence the ANS indirectly through inhibitory effects on the amygdala and directly through projections to both the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) (Thayer and Lane, 2009). Within the ANS, threat-related brain activity up-regulates SNS activity as indexed by peripheral vasoconstriction, increased blood pressure and greater release of the catecholamines norepinephrine and epinephrine from the adrenal medulla and norepinephrine from sympathetic nerves throughout the body (Blascovich and Mendes, 2010; Mendes et al., 2008). At the same time, threat perception downregulates the PNS, as indexed indirectly by decreases in respiratory sinus arrhythmia (Thayer et al., 2012; Thayer and Sternberg, 2009).

3.3. Threat perception and inflammation

Following these changes in the HPA axis and ANS, increased cortisol and catecholamines circulating in the blood can bind to receptors on immune cells and initiate intracellular signaling cascades that regulate immune cell gene expression and the release of inflammatory cytokines (Black, 2002; Padgett and Glaser, 2003; Sternberg, 2006; Thayer et al., 2011). In response to acute social-evaluative threat, activation of the HPA axis and ANS is accompanied by increased inflammation (Carroll et al., 2011; Dickerson et al., 2009a,b; Moons et al., 2010; Murphy et al., in press). Chronic threat perception appears to have similar effects; people living in a state of fear about specific threats (e.g., fear of terrorist acts), and individuals with a dispositional bias toward threat-related information (i.e., highly trait anxious and highly pessimistic individuals), have both been found to have elevated resting levels of inflammation (Melamed et al., 2004; O'Donovan et al., 2009; Pitsavos et al., 2006). Overall, this evidence suggests that threat-related activation of central and peripheral systems is accompanied by increased inflammation.

However, the mechanisms by which activation of the HPA axis and ANS permit or promote elevated inflammation are complex and incompletely understood. One complexity is that high doses of endogenous and synthetic glucocorticoids have well-documented anti-inflammatory effects (Auphan et al., 1995). Thus, the cortisol release following threat-related HPA axis activation should theoretically be associated with less, not more, inflammation. One explanation for this apparent paradox is that threat simultaneously *up-regulates* the HPA axis and increases cortisol production, while *down-regulating* the sensitivity of receptors for glucocorticoids on immune cells, thus reducing the extent to which cortisol can inhibit inflammation (Sheridan et al., 2000; Stark et al., 2002). Support for this hypothesis is provided by a human laboratory-based study that involved exposing individuals to an acute episode of social-evaluative threat. In this study, immune cells taken from participants who completed a stressful public speaking task in front of a socially rejecting panel of raters exhibited decreased sensitivity to the anti-inflammatory effects of glucocorticoids (Dickerson et al., 2009a). Mounting evidence also indicates that glucocorticoids can have pro- as well as anti-inflammatory effects, and that low levels of glucocorticoids are actually *required* for activation of the inflammatory response (Sapolsky et al., 2000; Sorrells and Sapolsky, 2007).

Activation of the ANS can also have both pro- and anti-inflammatory effects via the release of catecholamines and direct innervation of immune organs including the spleen, thymus, and lymph nodes (Bierhaus et al., 2003; Borovikova et al., 2000; Flierl et al., 2008; Röntgen et al., 2004; Sternberg, 2006; Thayer et al., 2011; Thayer and Sternberg, 2010; Tracey, 2002). The sympathetic arm of the ANS (SNS) can both inhibit and promote inflammation (Elenkov and Chrousos, 2006; Thayer and Sternberg, 2010). However, up-regulation of the SNS in anxious individuals is typically accompanied by down-regulation of the parasympathetic arm of the ANS (PNS), and reduced PNS activity has been associated with increased inflammation (Haensel et al., 2008). Moreover, lower PNS activity has been associated with elevated inflammation even when adjusting for the contributions of SNS activity (Thayer and Fischer, 2009). Thus, decreased PNS activity in threatened individuals may play a key role in permitting the elevated systemic inflammation observed in anxious

individuals. Fig. 3 illustrates some of the pathways that link threat-related neural activity with elevated inflammation.

4. Chronic anxiety and inflammation

Thus far, we have described threat-related changes in central and peripheral systems that have the ability to increase systemic levels of inflammation. It is important to note that these changes provide short-term protection against the potential physical harm associated with threatening events. Specifically, acute inflammation prevents infection, elicits pain to encourage avoidance of further injury, and up-regulates cellular (e.g., neutrophils, monocytes) and humoral (e.g., antibody, complement) immune processes targeted at removing pathogens and healing damaged or infected sites (Suffredini et al., 1999). Systemic inflammation also promotes behavioral changes, collectively known as *sickness behavior*, which resemble some symptoms of major depression (e.g., fatigue and anhedonia) and limit social-behavioral activity to reduce risk for further infection or injury (Dantzer et al., 2008). However, inflammatory activity must be down-regulated when no longer necessary. If sustained, elevated inflammation can have deleterious effects, increasing risk for clinical depression as well as for diseases of aging and early mortality (Cohen et al., 1997; Dantzer et al., 2008; Morrow et al., 1998; Pradhan et al., 2001; Strandberg and Tilvis, 2000; Volpato et al., 2001; Yin et al., 2004).

Anxiety-related increases in inflammation may be sustained across years or decades because the onset of many anxiety disorders occurs during sensitive periods in early life when biological systems develop, and because symptoms tend to persist over long periods of time (Danese et al., 2011; Hertzman, 1999; Prenoveau et al., 2011). There are several pathways by which anxiety-related exaggerated neurobiological sensitivity to threat could promote chronic inflammation. However, we will confine our discussion to four key neurobiological pathways: structural and functional brain changes; changes in receptor sensitivity; changes in basal HPA axis and ANS activity; and accelerated cellular aging.

4.1. Structural and functional brain changes

One pathway by which exaggerated threat sensitivity may lead to chronic inflammation is through changes in the brain regions involved in detecting and processing subsequently encountered threats (McEwen, 2007; Yirmiya and Goshen, 2011). Much of the evidence for these changes comes from studies showing changes in the structure and functional connectivity of the brain in the aftermath of adverse early life experiences that increase neurobiological sensitivity to threat (Tottenham and Sheridan, 2010). These neurobiological changes can be generated through *neural plasticity* and can involve alterations in the physical structure of the brain, changes in synapse turnover, dendritic remodeling or neuronal replacement, and alterations in functional activity or connectivity between target brain areas (McEwen et al., 2012). Importantly, accumulating evidence confirms that such alterations occur throughout the lifespan and not only in early life (Li et al., 2006).

The brain areas involved in detecting, processing, and remembering threatening information have dense catecholamine and glucocorticoid receptors, making them highly sensitive to the effects of repeated and prolonged activation of the HPA axis and ANS (Buffalari and Grace,

2007; Jöels, 2006; McEwen, 2010). As evidence for the fact that sustained activation of biological stress systems has neurotoxic effects, exposure to traumatic stress involving threat to life or physical integrity results in smaller hippocampal and mPFC volumes (Apfel et al., 2011; Rao et al., 2010; Shin et al., 2006), although possibly only in vulnerable individuals (Gilbertson et al., 2002; Gross and Hen, 2004). Connectivity in various brain circuits can change due to experience as well (Saibeni et al., 2005). For example, exposure to early life stress is associated with impaired connectivity between the amygdala and the right ventrolateral PFC (Robinson et al., 2012b). Such structural and functional brain changes are relevant for health because they can impair the regulation of central and peripheral responses to threat, promoting the sustained threat perception that may drive chronic inflammation.

4.2. Changes in receptor sensitivity

Sustained threat perception also changes how immune cells respond to signals from threat-related neuroendocrine and inflammatory factors. These changes can come about through altered sensitivity of immune cell receptors. For example, several studies have indicated that exposure to chronic stress down-regulates glucocorticoid receptors on immune cells, making them less sensitive to the anti-inflammatory effects of cortisol (Miller et al., 2002; Rohleder et al., 2009, 2010). In addition, bioinformatics and other approaches have revealed less signaling to immune cells via the glucocorticoid receptor in individuals who have a greater tendency to perceive ambiguous situations as threatening, specifically those who are socioeconomically disadvantaged during early life (Chen et al., 2004) or who develop PTSD in the aftermath of trauma (O'Donovan et al., 2011c). Thus, sustained threat perception in anxious individuals may down-regulate glucocorticoid receptors on immune cells, leading to a failure of the negative feedback effects of cortisol on threat-related inflammation.

4.3. Changes in HPA and ANS activity

In addition to influencing immune cell receptors for stress hormones, sustained threat perception may alter resting and reactivity levels of HPA axis and ANS activity. Many studies have documented elevated resting and reactivity levels of cortisol in patients with clinical anxiety disorders (Maes et al., 1998; Thayer, 2006; Thayer et al., 1995). However, there is also evidence that some anxiety disorders may be associated with lower resting levels of cortisol (O'Donovan et al., 2010; Thayer et al., 2009; Yehuda, 2009; Yehuda et al., 1990). Potential reasons for this lack of convergence in findings include differences across anxiety disorders and the absence of controls for circadian factors, comorbid psychiatric symptoms (such as depression), duration of anxious symptoms, or the inherent complexity of the HPA axis, which can become dysregulated at many levels. The relationship between anxiety and the SNS appears dependent on the timescale of particular analyses. A meta-analysis of relevant studies of acute stress indicates that anxious individuals exhibit hypoactive sympathetic responses to acute threat, but prolonged activation of the SNS when threats have passed (Chida and Hamer, 2008). Patients with anxiety disorders have shown lower PNS activity in most studies (Blechert et al., 2007; Sharma et al., 2011; Watkins et al., 1998), although not all (Davis et al., 2002). Large-scale studies that take timescale, circadian rhythms and comorbidities into account are needed to clarify the nature of dysregulation in the HPA axis and ANS in chronically anxious individuals.

4.4. Accelerated cellular aging

Sustained threat perception can also lead to elevated inflammation through an accelerated rate of cellular aging, as indexed by telomere shortening. Telomeres are DNA–protein complexes that cap the ends of chromosomes and protect against damage to the DNA that encodes our genes. Telomeres shorten with each cycle of cell division and with age, and immune cell telomere length is an emerging marker and mechanism of cellular aging (Blackburn, 2000; Sahin et al., 2011). Moreover, short telomere length confers increased risk for several major diseases of aging including cardiovascular, autoimmune, and neurodegenerative diseases, as well as for early mortality (Cawthon et al., 2003; Grodstein et al., 2008; Willeit et al., 2010). Individuals with high levels of threat sensitivity – as indexed by pessimism, childhood trauma exposure, phobic anxiety or post-traumatic stress disorder – have shorter telomere length (Kananen et al., 2010; O'Donovan et al., 2011a, 2009; Okereke et al., 2012; Surtees et al., 2011; Tyrka et al., 2010). Individuals experiencing various forms of chronic psychological stress also have shorter telomere length (Cherkas et al., 2006; Damjanovic et al., 2007; Epel et al., 2004), which appears to be mediated at least in part by increased threat perception (O'Donovan et al., 2012). Although accelerated cellular aging may be driven by elevated inflammation (Jaiswal et al., 2000), the relationship between inflammation and cellular aging is likely to be bidirectional, given that cells with short telomeres release higher quantities of proinflammatory factors such as IL-6 and TNF-α (Coppé et al., 2010; O'Donovan et al., 2011b). Thus, accelerated cellular aging may be a potential contributor to increased disease risk in anxiety, largely through threat-related elevated inflammation.

5. A neurobiological model of anxiety-related risk for diseases of aging

Based on the findings presented above, we propose a neurobiological model showing how anxiety disorders may promote the development of chronic diseases such as cardiovascular, autoimmune, and neurodegenerative diseases, and increase risk for early mortality (Fig. 4). In this model, exaggerated neurobiological sensitivity to threat in anxious individuals leads to cognitive-behavioral responses characterized by a pattern of vigilance-avoidance, which ultimately results in sustained threat perception. Accompanying this sustained threat perception is prolonged activation of threat-related neural circuitry and threat-responsive biological systems including the HPA axis, ANS, and inflammatory response. Over time, these effects on central and peripheral systems may become chronic through structural changes in the CNS, altered sensitivity of receptors on immune cells, and accelerated cellular aging, as well as through other pathways. As a consequence, chronically elevated inflammation can have toxic effects throughout the body and increase risk for early onset and accelerated progression of diseases of aging.

5.1. Implications for understanding stress and health

The proposed model has implications for understanding trends in public health such as upswings in disease during certain stressful periods, as well as in specific geographic regions and in individuals exposed to various forms of psychological stress (Cohen et al., 2009; Maunder et al., 1999; Seal et al., 2007, 2012). Although there are documented links between stress exposure and both physical and mental disease outcomes (Cohen et al., 2007;

Monroe et al., 2009), these associations are not easily deconstructed and remain understood only at the level of the global stress response. However, the apparently complex relationship between stressor exposure and disease might be understood in terms of threat sensitivity. Specifically, in stressful contexts, increased neurobiological sensitivity to threat at individual, community, or societal levels might increase risk for the early development of diseases of aging by increasing inflammation. Moreover, following such experiences, individual differences leave those predisposed to anxiety with persistently exaggerated threat sensitivity and systemic inflammation. Thus, even someone with an initially stable emotional temperament may develop an anxious style of emotional processing, driven by the neural changes described above (Bar-Haim et al., 2011a; Britton et al., 2011; Melamed et al., 2004; Pine et al., 2005). Subsequently, the tendency toward negative mood reactivity to daily life stress may promote biological stress responses and increase risk for the development of chronic physical diseases (Piazza et al., 2012). Variation in the degree of increase in threat sensitivity following exposure to psychological stress may explain why some people do and other people do not show increased risk for disease in the aftermath of stressful experiences.

5.2. Implications for treatment

The proposed model highlights several potential targets for pharmacological and psychological intervention. Although single-dose administration of selective serotonin reuptake inhibitors (SSRIs) may increase threat sensitivity (Browning et al., 2007; Grillon et al., 2007), longer term administration of commonly used psychopharmacological agents including SSRIs and selective noradrenaline reuptake inhibitors may reduce threat sensitivity (Harmer et al., 2006; Mogg et al., 2004; Murphy et al., 2009; Rawlings et al., 2010). Pharmacological interventions that target inflammation or HPA and ANS mechanisms involved in inflammation may be warranted as an adjunct or replacement for psychological interventions. However, the effectiveness of anti-inflammatory treatments for individuals with psychiatric disorders remains unclear (Miller et al., 2009; Warner-Schmidt et al., 2011), and both psychopharmacological and anti-inflammatory medications have adverse side effects. Thus, there are several potential pharmacological treatments that may target causal elements in our proposed model, but additional research is needed to assess their effects on disease risk in anxious individuals.

In the meantime, there is evidence that a number of existing and emerging cognitive-behavioral therapies (CBT) may be helpful. Different forms of CBT have been found to reduce threat-related cognitive-behavioral biases as well as pro-inflammatory signaling (Antoni et al., 2011; Beck, 1976; Smits et al., 2012). Prolonged exposure treatments that involve carefully titrated exposure to stimuli perceived as threatening may break the cycle of vigilance-avoidance in anxious individuals and thereby reduce inflammation (Foa, 2011). In recent years, computerized threat-related cognitive bias modification has emerged as an effective treatment that reduces threat-related attentional biases and anxiety (Bar-Haim et al., 2011b; Browning et al., 2010). Because such treatments may be effectively administered online, they may prove to be a targeted and cost-effective method for reducing anxiety-related disease risk (MacLeod et al., 2007). Lastly, extrapolating from a cross-sectional study, therapies targeted at increasing positive personal resources may dampen threat-related

neural activity through prefrontal cortex enhancement and decreased threat perception (Taylor et al., 2008).

5.3. Future research

Our review highlights that insufficient attention has been paid to the mechanisms of anxiety-related increased risk for chronic physical diseases. Although a large literature now exists linking depression and inflammation (Dantzer et al., 2008; Raison et al., 2006; Slavich and Irwin, submitted for publication; Slavich et al., 2010a), the relationship between anxiety and inflammation has received very little attention. In the present review, we emphasize common threat-related cognitive-behavioral biases across anxiety disorders and postulate that these biases have important effects on central and peripheral systems that regulate inflammation.

Although it is clear that different anxiety disorders confer increased risk for diseases of aging, threat-related biases take different forms across the anxiety disorders (Krusemark and Li, 2011), and further research is needed to clarify common and distinct patterns of responding to threat across diagnostic groups. In addition, there are unanswered questions regarding the association between threat and inflammation in anxious individuals. Some of the most pressing questions relate to specificity in the relationship between threat perception and inflammation (Kemeny, 2009). Previous research on threat-related activation of inflammation in humans has relied on manipulating the social environment to evoke threat-related responses (Carroll et al., 2011; Dickerson et al., 2009a; Moons et al., 2010). However, the inflammatory response may be activated by many different types of threat, ranging from phylogenetic threats (e.g., spiders, snakes), to contamination threats (e.g., open infected wounds, sneezing), to conspecific violence (e.g., angry aggressive humans). Although ethical concerns preclude research on some important categories of threat, the use of virtual reality technology permits the exposure of humans to a wide range of stimuli (e.g., war zones, deadly predators, infected wounds). Research examining common and specific responses to different forms of threat in anxious and non-anxious individuals will shed light on the applicability of our model across groups and situations. Moreover, it would be helpful to assess additional neurobiological and psychosocial aspects of anxiety disorders that may increase risk for physical disease across diagnostic groups or in specific anxiety disorders (e.g., social isolation, sleep disturbance, and health behaviors).

Our review also highlights a pressing need to identify the specific biological processes mediating inflammatory responses to threat. Although in vitro and non-human research may provide important information on these mechanistic processes, research with humans is also necessary because some types of threat – such as symbolic, imagined, or anticipated threats – appear unique to humans (Gilbert and Wilson, 2007). Although mechanistic research is limited in humans because genetic and pharmacological manipulations of biological pathways are seldom possible, developments in bioinformatics provide a partial solution to this problem as they permit researchers to probe large amounts of genomic, proteomic, and metabolomic data for underlying causal mechanisms. For example, the Transcription Element Listening System (TELiS) permits analysis of the intracellular signaling pathways underlying gene expression patterns of specific cell types (Cole et al., 2005). Of relevance to

the present review, research conducted with TELiS suggests that decreased anti-inflammatory signaling through the glucocorticoid receptor and increased pro-inflammatory signaling by nuclear factor-κB may underlie chronic stress and PTSD-related elevations in inflammation (Chen et al., 2011; O'Donovan et al., 2011c; van Vollenhoven, 2009).Thus, technological advances in the field of bioinformatics and increases in computing power may permit more detailed mechanistic understanding of the relationship between threat sensitivity and inflammation.

In addition, it is important to elucidate factors that moderate the effects of anxiety on inflammation and chronic disease risk. These moderating factors include social–environmental factors like childhood adversity that promote epigenetic changes and increase risk for anxiety (McEwen, 2010); genetic polymorphisms, such as the serotonin transporter polymorphism (5HTTLPR) and polymorphisms in the promoter of the pro-inflammatory interleukin-6 gene (rs1800795), which influence stress responding and inflammation (Cole et al., 2010; Hariri et al., 2005, 2002); and health behaviors that affect inflammation-related disease risk, such as voluntary sleep curtailment and physical inactivity (Puterman et al., 2011; Taylor et al., 2011). Thus, integrative multidisciplinary studies will be needed to uncover more specific treatment targets for the reduction of inflammation in sub-populations of anxious individuals.

We have drawn on several related lines of research in proposing our integrative neurobiological model and have presented evidence for each of the individual pathways in the model. To date, however, no studies have examined all of the pathways concurrently. As a result, there is no existing research evaluating our model as a whole. Such research would involve exposing individuals to different types of threat while monitoring their cognitive-behavioral, neural, and inflammatory responses. To our knowledge, only one study has examined neural processes underlying inflammatory responses to social threat. In this study, individuals who exhibited greater activation of the dACC and bilateral anterior insula in response to social rejection showed greater inflammatory responses to a subsequent episode of acute social stress (Slavich et al., 2010b). A complementary strategy for identifying causal mechanisms of anxiety-related inflammation involves manipulating specific factors in the model and analyzing the downstream consequences of such manipulations. One study that employed this approach used a cognitive-behavior stress management intervention to target anxiety-related affective and behavioral processes in a sample of patients with breast cancer. Results indicated that the intervention led to down-regulation of pro-inflammatory signaling to immune cells through NF-κB and reduced expression of genes that regulate pro-inflammatory factors (Antoni et al., 2011). Similar intervention studies that include analysis across cognitive-behavioral, neural, and inflammatory systems are necessary for advancing research on anxiety and health.

6. Conclusions

Drawing on research from cognitive psychology, neuroimaging, neuroendocrinology, and psychoneuroimmunology, we propose that exaggerated neurobiological sensitivity to threat is a key mediator of anxiety-related increases in inflammation, and that inflammation, in turn, promotes the development and accelerated progression of a variety of major diseases of

aging. This model identifies several psychological and biological processes that can become the target of interventions designed to reduce risk for disease in anxious individuals. The model also generates several testable hypotheses for future research. Coordinated biobehavioral responses to perceived threat are critical for ensuring fitness within dangerous environments. When threat perception is sustained as in the case of highly threat-sensitive anxious individuals, however, chronically elevated inflammation may promote the development and accelerated progression of diseases of aging and, shorten the lifespan. Given the high lifetime prevalence of anxiety disorders, and the substantial social and economic costs associated with anxiety-related physical disease, addressing anxiety-related health problems should be of paramount public concern.

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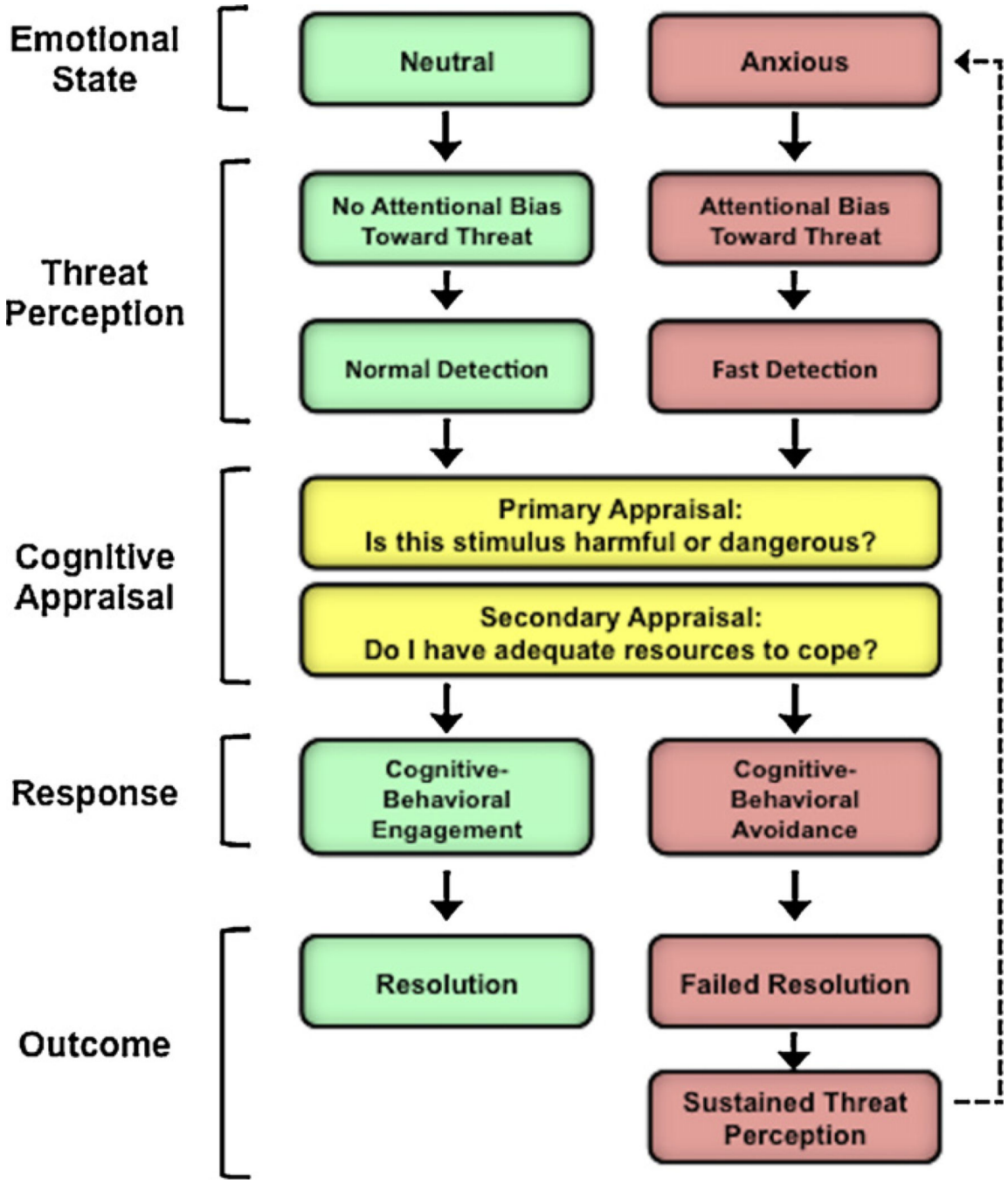

Fig. 1.

A broad overview of cognitive-behavioral responses to perceived threats in anxious and non-anxious individuals. Anxious individuals show cognitive biases toward threatening information, which leads them to detect threatening stimuli (e.g., angry faces or predatory animals) more quickly than non-anxious individuals, and to appraise both ambiguous and threatening stimuli as more threatening. Anxious individuals also show a tendency to engage in cognitive-behavioral avoidance, which limits their ability to challenge inappropriate threat perception, confront and resolve threatening situations, and reshape expectations for the

future. The ultimate result of this process is failure to achieve resolution of perceived threats, resulting in sustained threat perception.

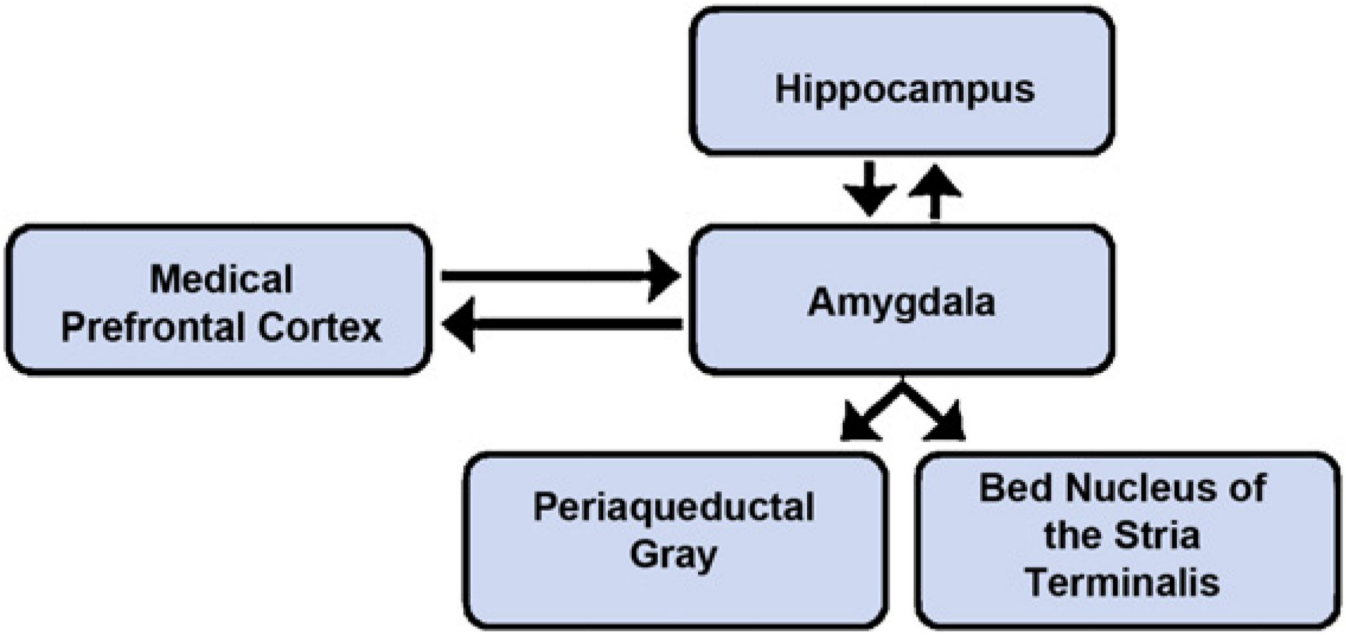

Fig. 2.

Hypothetical model of the neural systems involved in detecting threats, and regulating behavioral and biological responses to threat. Central to this network is the amygdala, which responds quickly to potential threats in the environment and plays a key role in determining whether environments are perceived as safe or dangerous. The amygdala functions in concert with other brain regions including the hippocampus and medial prefrontal cortex, which can up-regulate or down-regulate amygdalar responses to threat. Moreover, behavioral and biological responses to threat depend on activation of other brain areas, including the bed nucleus of the stria terminalis, which coordinates autonomic and motor responses to threat, and the periaqueductal gray, which coordinates stereotyped defensive reactions to threat, such as immobility and panic. Activity in this threat-related neural network is potentiated for individuals with anxiety disorders, as well as for persons exhibiting high levels of trait anxiety.

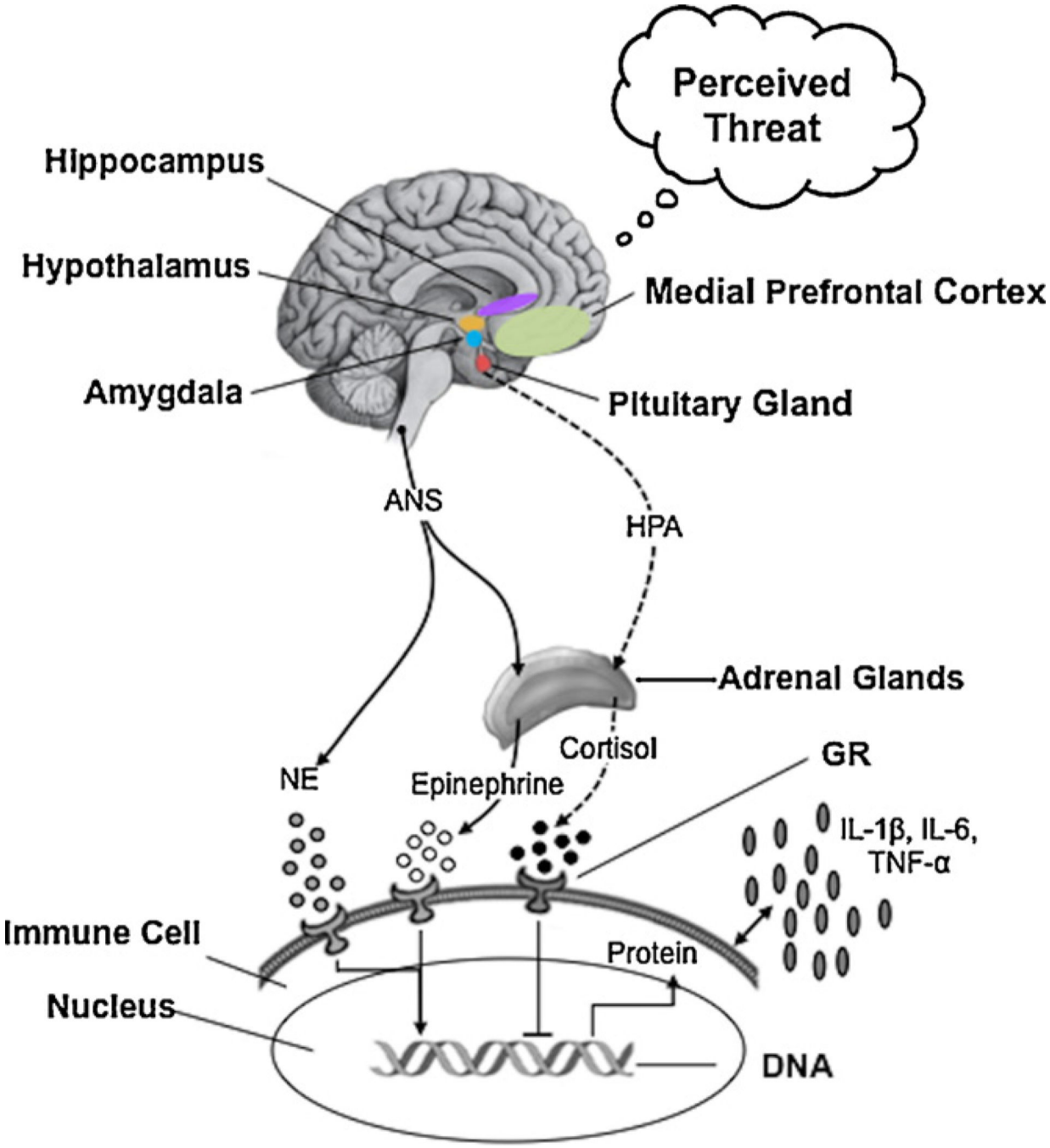

Fig. 3.

Illustration of the pathways linking threat-related neural activity in the amygdala, medial prefrontal cortex and hippocampus with elevated inflammation. Threat perception leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis leading to increased release of the glucocorticoid hormone cortisol from the adrenal glands (broken lines). Threat perception also activates the sympathetic arm and deactivates the parasympathetic arm of the autonomic nervous system (ANS), leading to increased release of the catecholamines epinephrine and norepinephrine (solid lines). This pattern of activation and deactivation is

accompanied by increased synthesis and release of pro-inflammatory cytokines including interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). Binding of these factors to receptors on immune cells regulates gene expression, including expression of genes for pro-inflammatory cytokines. Thus, the effects of the HPA axis and ANS on the immune system depend on the expression of immune cell receptors for cortisol and catecholamines, as well as on the release of these hormones. The glucocorticoid receptor (GR) appears to be down-regulated in response to threat, limiting the anti-inflammatory effects of cortisol. Although there are complex bidirectional relationships between the various factors in this model, threat perception ultimately leads to elevated inflammation.

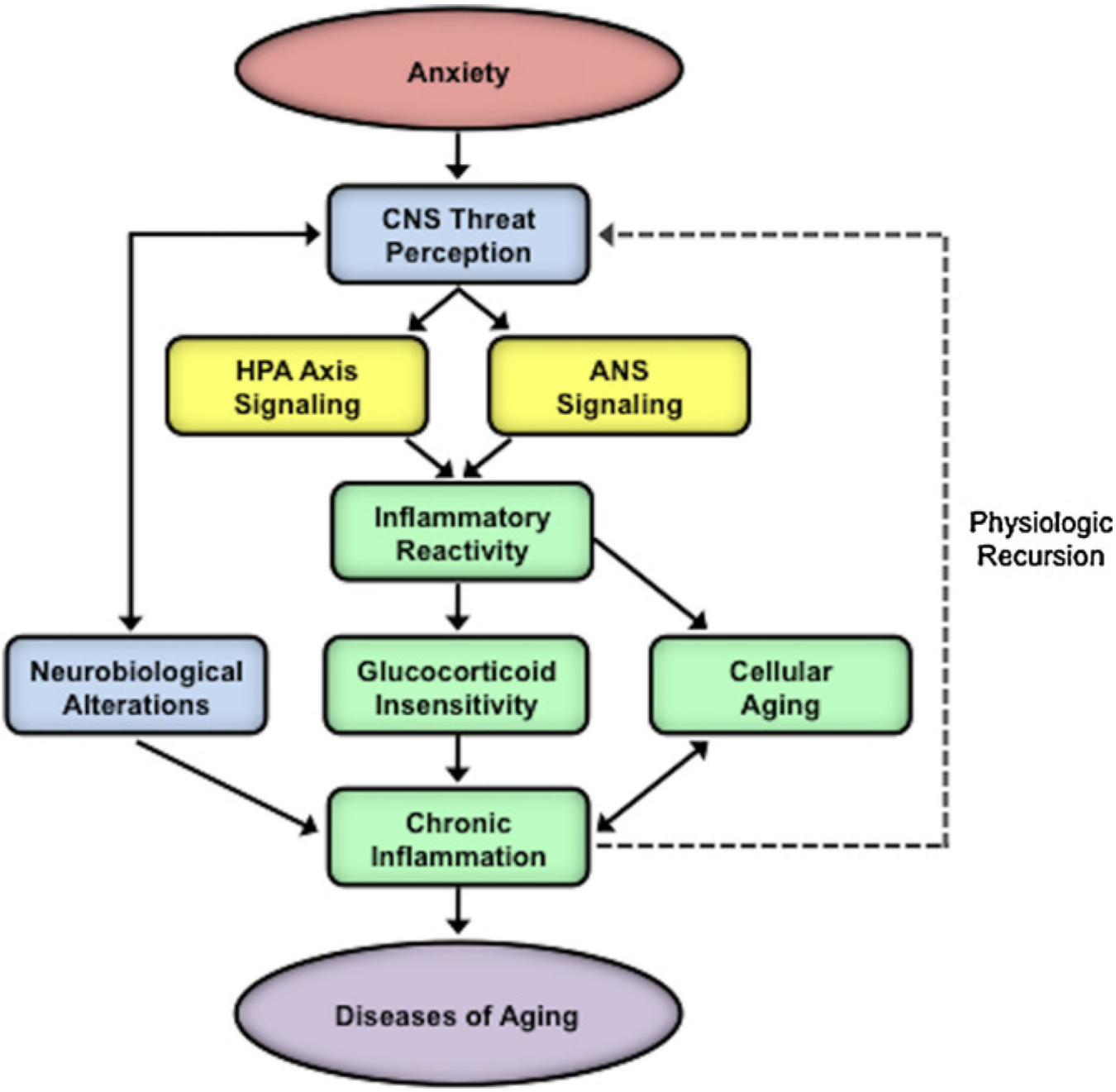

Fig. 4.

Integrative neurobiological model showing the pathways mediating anxiety-related increased risk for diseases of aging. The model depicts how exaggerated neurobiological sensitivity to threat in anxious individuals leads to cognitive-behavioral threat responses characterized by a pattern of vigilance-avoidance, which ultimately results in sustained threat perception. Such sustained threat perception is accompanied by prolonged activation of threat-related neural circuitry and threat-responsive biological systems including the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system (ANS), and inflammatory response, ultimately leading to elevated inflammation. Over time, the effects

on central and peripheral systems may become chronic through structural changes in the central nervous system (CNS), altered sensitivity of receptors on immune cells, and accelerated cellular aging. Finally, such chronic elevations in inflammation can increase risk for, and accelerate the progression of, diseases of aging.