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Review

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.

Contents

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Still, thou art blest, compar'd wi' me!
The present only toucheth thee:
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).