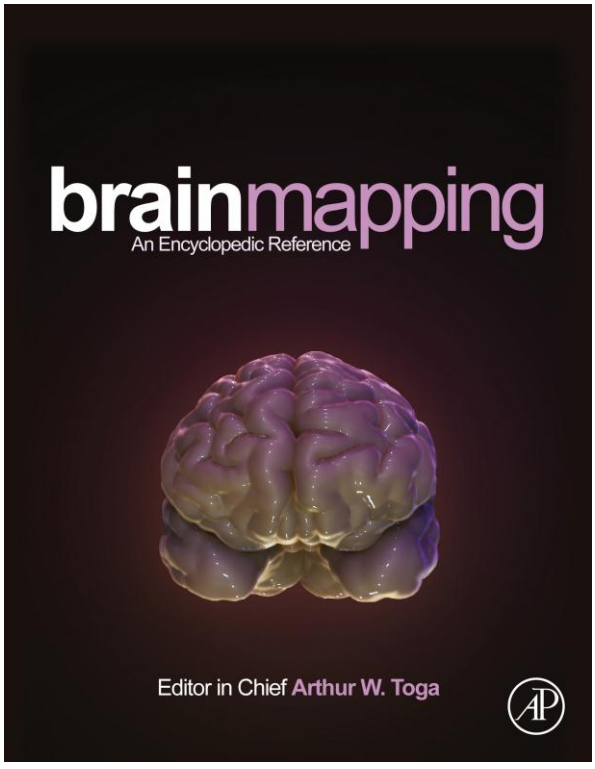

Muscatell K.A., and Eisenberger N.I. (2015) Neurocognitive and Physiological Mechanisms Linking Stress and Health. In: Arthur W. Toga, editor. *Brain Mapping: An Encyclopedic Reference*, vol. 3, pp. 29-33. Academic Press: Elsevier.

Neurocognitive and Physiological Mechanisms Linking Stress and Health

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Glossary

Autonomic nervous system Part of the peripheral nervous system that controls many vital functions such as respiration, heart rate, and blood pressure; activates during times of stress.
Cortisol A hormone released during times of stress that helps mobilize energy resources to help an organism 'fight' or 'flee.'
Pro-inflammatory cytokines Proteins that are secreted by immune cells as part of the innate immune response; key component of the body's first line of defense against injury or infection.
Social cognition Thinking about the thoughts, feelings, and beliefs of other people.

Across the United States in offices, classrooms, cafes, and dining rooms, a common refrain echoes when someone is asked about his or her current state: 'Stressed.' The modern world is full of psychological stressors, which can take a severe toll not only on an individual's moment-to-moment happiness but also on their physical health. For example, stress has been linked to the exacerbation of acute infections like the common cold (Cohen, Tyrrell, & Smith, 1991) and the development of chronic diseases, such as cardiovascular disease (Steptoe & Kivimaki, 2012).

But what are the physiological processes that are activated in the face of stress that can lead to these negative health outcomes? And what are the neural correlates of these stressor-evoked physiological changes? The purpose of this article is to provide a brief overview of recent research in 'health neuroscience,' a growing field that in part explores how both the brain and the body respond to stressors, with the ultimate goal of understanding the neurocognitive systems that may link stress and health. First, we provide some general background on the major physiological stress systems that have been studied in the context of health neuroscience. Then, we discuss neuroimaging research that has attempted to link neural activity during a stressor with physiological stress reactivity. Finally, we offer general conclusions and highlight outstanding questions to be addressed in future research.

Physiological Systems Linking Psychological Stress and Health

Arguably, the most important physiological system linking psychological stress and physical health is the immune system. Early research on stress and immunity focused on how stress may lead to changes in immune cells' ability to fight pathogens (i.e., cytotoxicity; Byrnes et al., 1998; Dopp, Miller, Myers, & Fahey, 2000) and how stress can cause flare-ups in latent viruses that are virtually harmless under nonstressful conditions (Glaser, Pearl, Kiecolt-Glaser, & Malarkey, 1994). More recently, investigators have begun to explore how psychological stress can lead to increases in inflammation, another key component of the immune system. Inflammation is typically measured by examining levels of proteins called 'proinflammatory cytokines' in blood samples. Proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are released by immune cells and are important for orchestrating the body's initial response to injury or infection. However, when inflammation becomes prolonged and widespread throughout the body, it can lead to the development or exacerbation of a variety of health problems, including asthma, arthritis, and cardiovascular disease (Jousilahti et al., 2002; Libby, 2008; Ridker, Hennekens, Buring, & Rifai, 2000). Furthermore, levels of inflammation have been shown to increase in response to purely psychological threats (i.e., when there is no physical insult to the body; Steptoe, Hamer, & Chida, 2007), suggesting the possibility that stress may lead to disease in part via increases in inflammation.

But how do stressors lead to inflammation? Two primary systems are thought to link psychological stress and increases in inflammation: the autonomic nervous system (ANS) and the neuroendocrine system. The ANS is divided into two primary branches: the sympathetic nervous system (SNS), which tends to activate during a stressor, and the parasympathetic nervous system (PNS), which tends to disengage during stress. Many of the common 'symptoms' of stress, including sweaty palms, racing heart, and shortness of breath, are evidence of SNS activation and PNS withdrawal. However, it is impossible to disentangle the precise contributions of the SNS and PNS to changes in typically measured ANS indicators such as heart rate and blood pressure, so henceforth, we often refer to 'ANS' without specifying which particular 'branch' of this system is engaged. ANS activation is important for helping us meet the demands of a stressor in the short term, by directing our attention to important features of the situation, shutting down nonvital functions in the body (like reproduction and digestion), and mobilizing our energy stores to cope with the crisis. However, if a person is repeatedly activating the ANS, possibly even during ambiguous or not overtly stressful circumstances, or failing to shut down the ANS in an efficient manner, then ANS activation may lead to inflammation, starting a cascade toward poor health.

In addition to the ANS, the neuroendocrine system, and, specifically, the hypothalamic–pituitary–adrenal (HPA) axis, is another important stress-related physiological system that can contribute to inflammation. HPA axis activity results in the release of cortisol into the bloodstream, a hormone that is important for our ability to mobilize energy so we can 'fight' or 'flee' during a stressful situation. In the short term, cortisol actually has anti-inflammatory effects, causing immune cells to shut down their production of proinflammatory cytokines. However, if the HPA axis is chronically active, then immune cells may lose their ability to 'hear' a signal from cortisol and will continue to produce proinflammatory cytokines (a process called 'glucocorticoid resistance'; Miller et al., 2008). In this way, HPA axis activation can lead to increases in inflammation and possibly contribute to the development of disease.

While inflammation, ANS activation, and HPA axis activity are important physiological mediators of the relationship between stress and health, it is not the case that everyone who experiences stress develops a chronic disease (Chen & Miller, 2012), and there are substantial differences in the degree to which people show activation of these physiological systems when faced with a stressor (Davis, Donzella, Krueger, & Gunnar, 1999; Mendes, Blascovich, Lickel, & Hunter, 2002). This begs the question: Are there particular neurocognitive systems that, when engaged during a stressful experience, are likely to lead to physiological activation? A number of studies over the past 15 years have sought to answer this question, employing both functional MRI (fMRI) and positron emission tomography (PET) to measure neural activity and a variety of peripheral measures to index ANS, HPA, and inflammatory activation. Here, we review results from these studies, focusing on three particular neural 'systems' that are relevant in the context of stress: a threat-related system, a self/social cognition system, and safety-related system (see **Figure 1**; Muscatell & Eisenberger, 2012).

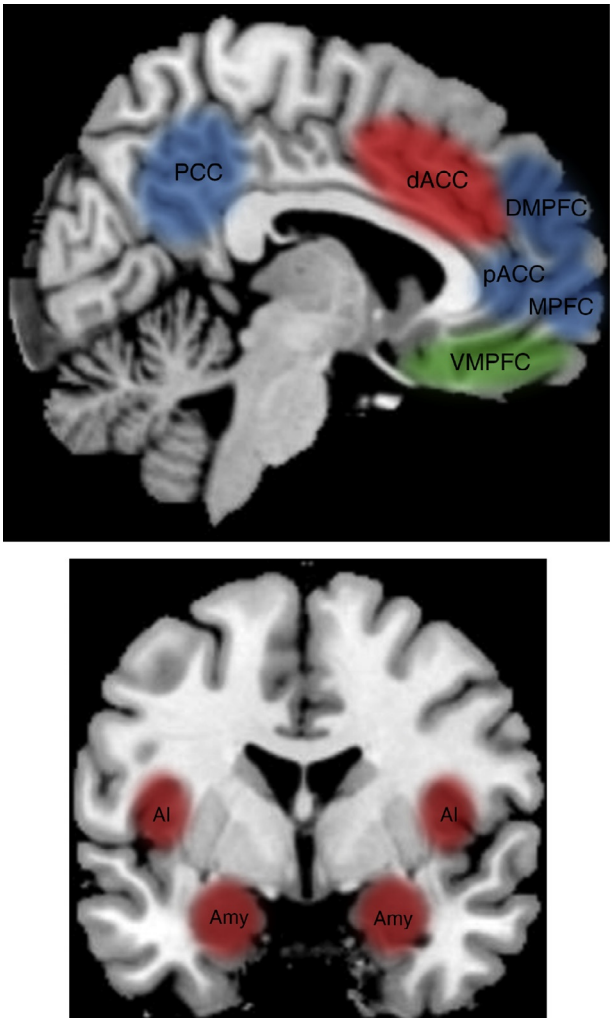

Figure 1 Visual schematic of the three primary neural systems that have been shown to play a role in stressor-evoked physiological responses: a threat-related neural system, made up of the dACC, AI, and amygdala (displayed in red); a safety-related neural system, made up of the VMPFC (displayed in green): and a self/social cognition-related neural system, made up of the MPFC, pACC, DMPFC, and PCC (displayed in blue). Adapted from Muscatell, K. A., & Eisenberger, N. I. (2012). A social neuroscience perspective on stress and health. *Social and Personality Psychology Compass*, *6*, 890–904.

The Threat-Related Neural System and Physiological Stress Responses

The threat-related neural system is made up of, among other regions, the amygdala, the dorsal anterior cingulate cortex (dACC), and the anterior insula (see **Figure 1**, regions displayed in red). These regions have been shown to activate during tasks that involve detecting and responding to threats in the environment, including negative faces and scenes (Adolphs, 2008), physically painful shocks and heat stimulations (Apkarian, Bushnell, Treede, & Zubieta, 2005), and experiences of social rejection (Eisenberger, 2012). Given that threat is a key 'ingredient' in what we call stress (Mendes et al., 2002; O'Donovan et al., 2012), these regions are likely to play an important role in processing and responding to a stressor. Furthermore, the amygdala and dACC may be especially relevant in relating to stressor-evoked increases in physiological activation, as both regions are highly connected with other, more 'basic' brain structures (such as the locus coeruleus and hypothalamus) that are important in initiating ANS and HPA axis activation (LeDoux, 2000; Ulrich-Lai & Herman, 2009). The anterior insula, on the other hand, may primarily be involved with representing stressor-evoked changes in the physiological state of the body in conscious awareness (Craig, 2009).

Is there evidence that activation of the threat-related neurocognitive system during a stressor is related to increases in physiological activation? A number of studies, primarily those investigating the neural correlates of stressor-evoked increases in ANS activation, provide data suggesting that activation in the amygdala, the dACC, and the anterior insula is indeed associated with increases in a number of indices of ANS activity. For example, a recent meta-analysis (Beissner, Meissner, Bar, & Napadow, 2013) suggests that all three regions of the threat system are associated with increases in skin conductance (a typical measure of the SNS branch of the ANS), as assessed during a variety of challenging cognitive and emotional tasks. A body of research examining stress-related increases in other indices of ANS activation (e.g., pupil dilation, heart rate, and mean arterial pressure) shows that neural

activity in the dACC during stressful tasks is related to increases in ANS activation (e.g., Critchley, 2005; Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Gianaros, van der Veen, & Jennings, 2004; Gianaros, Derbyshire, et al., 2005; Wager, van Ast, et al., 2009; for a full list, see Muscatell & Eisenberger, 2012). There is also evidence that activity in the anterior insula during a stressful cognitive task is related to increases in ANS activity (e.g., Critchley et al., 2000; Gianaros, Jennings, Sheu, Derbyshire, & Matthews, 2007; Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2011; Gianaros et al., 2008). The amygdala has also been shown to play a role in ANS responses to stress (e.g., Gianaros et al., 2008, 2011), though some studies find amygdala activity associated with decreases in ANS activity (Critchley et al., 2000; Gianaros et al., 2004). In sum, regions of the threat-related neurocognitive system, perhaps especially the dACC and anterior insula, are associated with stress-related increases in the activation of the ANS.

There are far fewer studies linking neural activity during stress and HPA axis or inflammatory responses, but of those that have been conducted, a subset find that activation of the threat-related neurocognitive system is associated with cortisol and inflammatory increases. For example, two studies have found that individuals who show greater activity in the dACC in response to a social stressor also mount a stronger cortisol response to stress (Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007; Wang et al., 2005). Only two known studies have investigated the neural correlates of inflammation responses to stress, and both find evidence that activation in regions of the threat-related neurocognitive system is associated with increases in inflammation (Muscatell et al., in press; Slavich, Way, Eisenberger & Taylor, 2010). Thus, though still in its infancy, the literature linking neural activity during stress and HPA axis/inflammatory responses points to the possibility that activity in the dACC and anterior insula, key regions of the threat-related neural system, is an important predictor of cortisol and inflammatory responses.

The Self/Social Cognition Neural System and Physiological Stress Responses

While the threat-related neurocognitive system plays an important role in responding to stress and linking with physiological activation, other brain systems are also involved. A second key 'network' involves a number of regions that are commonly activated during tasks that involve thinking about the self and the traits, thoughts, and feelings of others. These regions include the dorsomedial prefrontal cortex (DMPFC), the medial prefrontal cortex (MPFC), the pregenual anterior cingulate cortex (pACC), and the posterior cingulate cortex (PCC), which together make up a 'self/social cognition' system (see **Figure 1**, regions displayed in blue; Krienen, Tu, & Buckner, 2010; Lieberman, 2010; Mitchell, 2009). Negative self-related cognitions (e.g., low self-esteem) and emotions (e.g., shame) are both related to heightened physiological responses to stress (Dickerson, Kemeny, Aziz, Kim, & Fahey, 2004; Gruenewald, Kemeny, Aziz, & Fahey, 2004), and stressors that involve being evaluated by others are especially likely to lead to increases in physiological output (Bosch et al., 2009; Dickerson & Kemeny, 2004). Therefore, it stands to reason that activity in neural regions that underlie these psychological processes would be related to stressor-evoked changes in physiological activation.

Along these lines, activity in the MPFC, pACC, and PCC during a stressful task has been associated with increases in ANS activation and, though less consistently, cortisol responses. The most consistent evidence for the relationship between the self/social cognition system and ANS activation comes from a body of work by Gianaros and colleagues. In these studies, individuals complete a difficult cognitive task while receiving negative feedback that they have completed the task incorrectly the majority of time. Across a number of studies, neural activity in the MPFC, pACC, and the PCC during this stressful task is related to increases in a variety of ANS measures, including increases in blood pressure (Gianaros et al., 2007; Gianaros, May, Siegle, & Jennings, 2005) mean arterial pressure (Gianaros, Derbyshire, et al., 2005; Gianaros et al., 2008) and baroreflex suppression (Gianaros et al., 2011). Complimenting these findings is work that has explored neural and heart rate responses to a more 'socially stressful' task, in which participants prepare to give a speech they believe they will have to deliver to a panel outside of the scanner (Wager, Waugh, et al., 2009). Once again, greater neural activity in one of the key self/social cognition regions (i.e., pACC) during speech preparation was related to greater increases in heart rate. Together, these data suggest that responsivity of brain regions often active during tasks that involve thinking about the self and others is associated with increases in ANS activation during a stressor. Interestingly, this relationship is observed even when individuals are asked to complete tasks that do not explicitly ask them to think about themselves or others, suggesting the possibility that even stressful cognitive tasks may lead to physiological activation primarily to the degree that they elicit cognitions related to the self or others in the environment.

While this relatively large body of literature converges on a role for the self/social cognition system in relating to increased ANS activation during a stressor, results from studies investigating cortisol responses to stress are more mixed, with some studies finding a positive correlation between activity in these neural regions and cortisol output and other studies finding a negative or no relationship. Most work in this area has explored neural and neuroendocrine responses to social stressors, such as being socially rejected (Eisenberger et al., 2007) or being negatively evaluated by an experimenter or confederate during a performance task (Dedovic et al., 2009; Kern et al., 2008; Pruessner et al., 2008; Wang et al., 2005). The specific region in the self/social cognition network most consistently associated with increased cortisol responses is the DMPFC (Dedovic et al., 2009; Eisenberger et al., 2007), which is commonly activated when individuals are asked to think about others (Frith & Frith, 2006; Lieberman, 2010). Other studies find activity in MPFC (Wang et al., 2005) and PCC (Wang et al., 2005) related to greater cortisol reactivity. At the same time, one study reports greater activity in MPFC and pACC associated with *lower* cortisol reactivity (Pruessner et al., 2008), while another finds different subregions within the pACC to be positively and negatively correlated with cortisol responses (Kern et al., 2008). Thus, given the relatively small number of studies in this area and mixed findings, we are unable to draw firm conclusions regarding the role of the

self/social cognition system in cortisol responses to stress. Initial evidence suggests that some regions of this network may be related to greater cortisol reactivity, but more research is needed to fully map the neural systems engaged during stress that are related to cortisol responses. Among studies investigating neural and inflammatory responses to stress, one study finds activity in the PCC to be related to inflammation (Slavich et al., 2010), while another finds that stronger coupling between a threat-related region (i.e., amygdala) and a self/social cognition region (i.e., DMPFC) is related to greater inflammatory responses to stress (Muscatell et al., in press). Thus, the precise role this system plays in relating to inflammatory responses to stress is currently unclear.

The Safety-Related Neural System and Physiological Stress Responses

The final neural system that has been related to physiological stress responses is a 'safety-related system,' made up primarily of the ventromedial prefrontal cortex (VMPFC; see **Figure 1**, region displayed in green). The VMPFC is thought to be involved in general reward-related processing (Kringelback, 2005), and along these lines, activity in this region has been observed in studies that examine neural responses to cues of relative safety and security (which presumably are rewarding), such as when individuals view objects that previously elicited fear but are now considered safe (Schiller & Delgado, 2010) or when people look at pictures of loved ones while undergoing a painful experience (Eisenberger et al., 2011). Thus, VMPFC activity may reflect the perception that one is safe and supported, which we would expect to be related to *decreased* physiological responses to stress.

A number of studies of both ANS and cortisol responses to stress find support for the hypothesis that greater activity in VMPFC during a stressor is related to lower physiological reactivity. Indeed, increased activity in VMPFC during a difficult cognitive task or a social evaluative stressor is related to smaller stressor-evoked increases in mean arterial pressure (Critchley et al., 2000), heart rate (Wager, van Ast, et al., 2009; Wager, Waugh, et al., 2009), cardio acceleration (Gianaros, van der Veen et al., 2004), and cortisol (Eisenberger et al., 2007; Pruessner et al., 2008). In other words, to the extent that individuals activate this region that responds to cues of safety and security despite the fact that they are undergoing a stressor, they show lower physiological reactivity to the stress task. These results raise the intriguing possibility that VMPFC activity may reflect some degree of 'resilience' to the physiological stress response, though at this point, it is unclear what underlying neurocognitive processes this neural activity reflects. Future studies could explicitly manipulate perceptions of safety and security during stress (by showing pictures of support figures or reminders of positive self-characteristics) and examine if such conditions are associated with greater VMPFC activity and less physiological activation.

Conclusions and Future Directions

In sum, research that has investigated the neural systems involved in physiological responses to stress suggests that neural systems involved in processing threat, thinking about the self and others, and responding to safety cues are associated with physiological stress reactivity. Activation in regions that have been shown to respond to threat (i.e., dACC, anterior insula, and amygdala) and self/social cognition (i.e., DMPFC, MPFC, pACC, and PCC) during a stressor is related to greater physiological responding, while activity in a region that is involved in processing safety and rewarding experience more generally (i.e., VMPFC) is related to lesser physiological reactivity. Though there are only a few studies in this area, this growing literature is moving beyond simply mapping the brain areas that are engaged during stress to examining how those regions link with physiological responses, thus providing important clues regarding the neurocognitive processes that may link stress and health.

Given this current landscape of research in health neuroscience, what should be the focus of future research investigating the neurocognitive systems linking stress and health? First, more studies are needed that explore the neural correlates of neuroendocrine and inflammatory responses to stress, given that there are only six studies to date that have addressed both of these levels of analysis. It will also be important for future work to develop additional scanner-compatible stress tasks and to compare across different types of stress tasks, given that most studies thus far have used either challenging cognitive tasks (i.e., the Stroop task and difficult mental arithmetic) or social-evaluation tasks (i.e., preparing a speech and being socially excluded). Thus far, it seems that both types of tasks lead to similar brain–body relationships, but there are no direct comparisons between these types of stressors, and it will be important for future studies to disentangle the extent to which these different types of stress elicit similar or different neural and physiological responses. Finally, it will also be important to explore how the neural systems involved in physiological stress responses are related to clinically relevant outcomes (e.g., atherosclerosis in cardiovascular disease, tumor progression in cancer, and pain perceptions in rheumatoid arthritis), in an effort to link this neural activity and its physiological correlates with actual health outcomes.

See also: **INTRODUCTION TO CLINICAL BRAIN MAPPING**: Emotion and Stress; **INTRODUCTION TO SOCIAL COGNITIVE NEUROSCIENCE**: How the Brain Feels the Hurt of Heartbreak: Examining the Neurobiological Overlap Between Social and Physical Pain.

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