



A Social Neuroscience Perspective on Stress and Health

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Abstract

Psychological stress is a major risk factor for the development and progression of a number of diseases, including cardiovascular disease, cancer, arthritis, and major depression. A growing body of research suggests that long term, stress-induced activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis may lead to increases in inflammation, which is known to play a key role in the pathophysiology of a variety of diseases. Furthermore, the burgeoning fields of social neuroscience and health neuroscience have begun to identify the neurocognitive mechanisms by which stress may lead to these physiological changes. Here we review the literature examining the neurocognitive correlates of stress-induced SNS, HPA, and inflammatory responses. Specifically, we summarize the results of neuroimaging studies that have examined the neural correlates of stress-related increases in SNS, HPA, and inflammatory activity. A set of neural systems involved in threat processing, safety processing, and social cognition are suggested as key contributors to stress-related changes in physiology. We conclude by offering suggestions for future research in the exciting new field of health neuroscience.

“Of course it is happening inside your head, Harry,
but why on earth should that mean that it is not real?”
Harry Potter and the Deathly Hallows by J. K. Rowling

Psychological stress is commonplace in modern life. Within a day, a person is likely to endure many types of stressful experiences: From minor stressful events, such as giving a presentation at work or taking a midterm exam, to major life events, such as a serious argument with a partner or the loss of a job. All of these stressors can take place against a backdrop of chronic stress, such as serious financial debt or ongoing relationship difficulties. Indeed, stressful experiences are the norm, not the exception, in the lives of most individuals.

Far from being a mere nuisance that may impact our feelings of happiness, stress contributes to disease risk and early mortality. Indeed, stress has been linked with the development or progression of a number of major diseases, including cardiovascular disease, cancer, arthritis, and major depression (Cohen, Janicki-Deverts, & Miller, 2007; Juster, McEwen, & Lupien, 2010; Slavich, O'Donovan, Epel, & Kemeny, 2010a). The past 30 years of research have seen important developments in our understanding of the physiological mechanisms that may explain *how* stress influences health. These studies generally point to pathways that include stress-related activation of the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis, which can alter inflammatory processes – a correlate of many chronic diseases of aging (Gruenewald, Seeman, Ryff, Karlamangla, & Singer, 2006; Miller, Chen, & Cole, 2009). Although there are many remaining questions about the precise physiological mechanisms by which stress affects health, we have now made significant progress in understanding the physiological mediators of the stress-health link.

Less is known, however, about the central neurobiological mechanisms that may lead to stress-related physiological responses in humans. Understanding how stress is represented in the brain and how neural activity during stress relates to physiology is important, as the brain is the key organ of stress perception, appraisal, and coping processes (e.g., McEwen & Gianaros, 2010), and thus any complete model of stress-health mediators must include the brain. The availability of neuroimaging tools together with a growing understanding of the neural systems involved in a variety of social, affective, and cognitive processes (Dalglish, Dunn, & Mobbs, 2009; Lieberman, 2010; Singer, 2012) have coalesced to provide an opportunity to investigate the neural correlates of physiological stress responses.

Capitalizing on this opportunity, recent studies in “health neuroscience” have been conducted attempting to link physiological indicators with measures of neural activity during stress (Critchley, 2005; Gianaros & Sheu, 2009). In the present paper, we review the literature that has examined the neural correlates of stress-related changes in physiology. First, we identify and review the target physiological systems that have been linked with stress and health, as well as the neural systems that may be related to physiological stress responding. Then, we review and synthesize the results from neuroimaging studies that have examined stressor-evoked physiological responses. Finally, we offer suggestions for future research in the exciting new field of health neuroscience.

Overview of Physiological Stress Systems

The human body contains a number of physiological systems that have been implicated in stress and disease. One of the most critical systems is the inflammatory component of the immune system. Inflammation is the “first line of defense” the immune system triggers when we experience an injury or illness, making it an important component of healing and containment of disease. This process is carried out by pro-inflammatory cytokines, which are proteins that serve as the main orchestrators of the inflammatory response. Inflammation is critical for wound healing and preventing the spread of infection. However, exaggerated, repeated, or prolonged inflammatory activation can, over time, increase risk for disease and early mortality (Finch, 2010; McEwen, 1998). Indeed, inflammatory processes have been shown to contribute to the development of cardiovascular disease, rheumatoid arthritis, and asthma (Fahy, 2009; Libby, 2008; Taube, Schlick, Sell, Eckardt, & Eckel, 2012). Importantly, inflammatory responses are regulated by the SNS and the HPA axis, which activate in response to stressors.

The SNS is one branch of the autonomic nervous system, and, generally speaking, markers of SNS activity increase in response to psychological stress (Bradley, Miccoli, Escrig, & Lang, 2008; Nater & Rohleder, 2009; Uchino, Cacioppo, Malarkey, & Glaser, 1995). Other correlates of SNS activity, including heart rate and blood pressure, are also often measured in the context of stress (though increases in heart rate and blood pressure reflect some combination of sympathetic increases and parasympathetic decreases and are thus not solely driven by SNS activity). Numerous studies have shown that psychological stressors such as public speaking or interpersonal conflict evoke increases in blood pressure and heart rate (Kamarck & Lovallo, 2003; Smith et al., 2009). Furthermore, activation of the SNS has been linked to increased inflammation (Grebe et al., 2010; Irwin & Cole, 2011; Levick, Murray, Janicki, & Brower, 2010), suggesting that one mechanism by which SNS activity affects health is via increasing levels of inflammation.

Another regulator of inflammatory activity is the HPA axis. The hormone cortisol is the end product of activation of the HPA axis, and acute stressors are likely to elicit increases in cortisol. Interestingly, a meta-analysis that investigated cortisol responses to stress found that two features of stressors – uncontrollability and social-evaluation – were especially likely to be associated with increases in cortisol (Dickerson & Kemeny, 2004). Stressor-evoked elevations in cortisol are important for energy mobilization to deal with impending threats; however, elevated levels of cortisol may also lead to deleterious health outcomes via associated increases in inflammation. Although cortisol typically has anti-inflammatory effects, chronic activation of the HPA axis can lead to a condition called glucocorticoid resistance where immune cells no longer “hear” a cortisol signal (Miller et al., 2008), thus leading to increases in both cortisol and inflammation. As with SNS activation, HPA activation may ultimately affect health via its influence on inflammation.

Overview of Stress-Related Neural Systems

Here, we review several neural “systems” that may be relevant for stress-related physiological responding, including those involved in threat processing, safety processing, and self and social cognitive processing.

Neural circuitry involved in threat processing

In order for environmental circumstances or cues to be considered “stressful”, a potential threat must be detected by and represented in the brain. A number of neural regions including (but not limited to) the amygdala, the dorsal anterior cingulate cortex (dACC), and the anterior insula (AI) are thought to make up a basic “neural alarm system” that detects potential threats in the environment and coordinates responses to such threats (Eisenberger, 2012b; Eisenberger & Cole, 2012; Eisenberger & Lieberman, 2004; see Figure 1). Activity in threat-related neural regions may be related to physiological responses to stress, especially insofar as appraisals of threat are linked to increased physiological reactivity (Blascovich & Mendes, 2010; O’Donovan et al., 2012).

Arguably the most well known structure within the neural threat processing system is the amygdala. The amygdala is thought to respond to stimuli that are especially relevant for the goals and motivations of the perceiver (Cunningham & Brosch, 2012). Thus, the amygdala is often active in studies involving threat and fear (Phelps, 2006; Whalen, 2007), given that these types of stimuli are expected to be especially salient. The amygdala likely leads to increases in SNS activity via its connections with brainstem regions, such as the locus coeruleus (LC; Herman et al., 2003; Ulrich-Lai & Herman, 2009), a key region for norepinephrine production. Amygdala activation may trigger HPA responses via projections to the bed nucleus of the stria terminalis, which provides a link between the amygdala and the paraventricular nucleus (PVN) of the hypothalamus (Herman & Cullinan, 1997; LeDoux, 2000). PVN neurons secrete corticotrophin releasing hormone, which begins the cascade eventually leading to cortisol production.

A second important brain region in the threat processing system is the dACC. Activity in the dACC is correlated with the distressing feelings experienced during threat or pain, including physical pain (e.g., experiencing painful electric shocks; Apkarian, Bushnell, Treede, & Zubieta, 2005), and social pain (e.g., being excluded from a group; Eisenberger, 2012a). At the broadest level, the dACC is also involved in detecting the need for cognitive control (e.g., conflict monitoring, error processing; Egner, 2011; Schulz, Bedard, Czarnecki, & Fan, 2011), such as when relevant goals are not being met. Acute

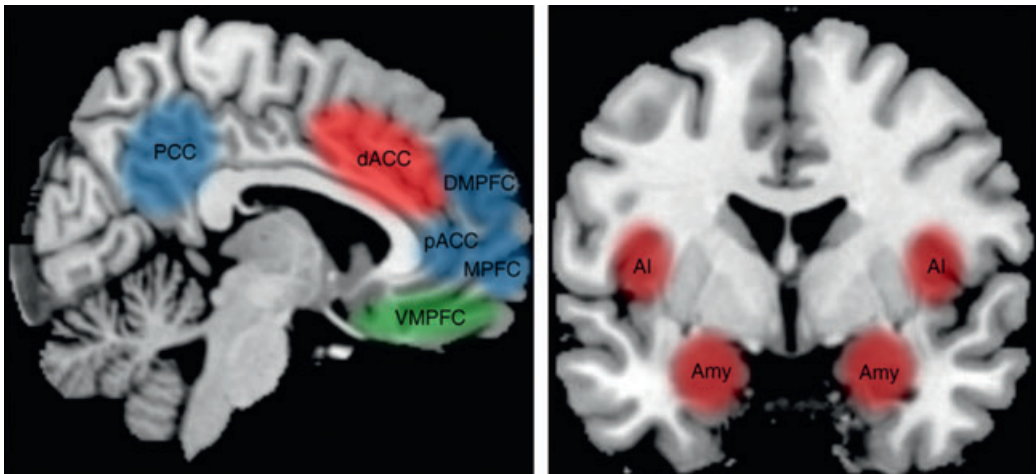


Figure 1 Schematic of neural regions that influence physiological responses to stress. Three primary neural systems have been shown to play a role in stressor-evoked physiological responses: a threat-related neural system, made up of the dorsal anterior cingulate cortex (dACC), anterior insula (AI), and amygdala (Amy; displayed in red), a safety-related neural system, made up of the ventromedial prefrontal cortex (VMPFC; displayed in green), and a self/social cognition-related neural system, made up of the medial prefrontal cortex (MPFC), perigenual anterior cingulate cortex (pACC), dorsomedial prefrontal cortex (DMPFC), and posterior cingulate cortex (PCC; displayed in blue).

stressors, which demand effortful, goal-directed behavior, may require these types of processes, and may thus involve dACC activity. The dACC is hypothesized to play a role in generating SNS responses via its connections with the amygdala (LeDoux, Iwata, Cicchetti, & Reis, 1988), which projects to the LC and initiates production of norepinephrine. Furthermore, the dACC may lead to HPA activity through its projections to the hypothalamus, which initiates CRH production and starts the HPA axis cascade (Burgos-Robles, Vidal-Gonzalez, & Quirk, 2009; Gabbott, Warner, Jays, Salway, & Busby, 2005).

Finally, the AI is also considered a component of the threat processing neural system. The insula is thought of as a key region for interoceptive awareness, or the conscious representation of the physiological condition of the body (Craig, 2009). In the context of stress research, activation of the AI is hypothesized to represent afferent outputs from physiological systems activated by stress or arousal (Critchley, 2005). Thus, activity in the AI is thought to reflect awareness of physiological changes that have taken place in the body.

Neural circuitry involved in safety processing

While perceptions of threat relate to greater physiological stress responses, perceptions of safety and security may be related to lesser physiological stress responses. Evidence from behavioral research suggests that the presence of social support during a stressor, which may signal safety and security, is related to less physiological reactivity (for a meta-analysis, see Thorsteinsson & James, 1999). Thus, neural regions involved in the processing of safety and security may also be related to reduced physiological stress responses.

Prior neuroimaging research suggests that the ventromedial prefrontal cortex (VMPFC) is involved in processing safety and inhibiting threat-related responding (see Figure 1). Activity in VMPFC is observed during fear extinction when a previously feared cue is subsequently associated with safety (Schiller & Delgado, 2010). Inhibitory connections

Table 1 Neural regions associated with physiological stress responses

Citation	Physiological measure	dACC	AI	Amygdala	MPFC (BA 10)	DMPFC	pACC	PCC	VMPFC
<i>Sympathetic-related responses</i>									
Critchley (2005)	Pupil dilation	+							
Critchley et al. (2003)*	LF-HRV	+	+						
Critchley et al. (2000)*	MAP	+						-	
Critchley et al. (2000)*	Heart rate		+	-					
Wager et al. (2009a)	Heart rate						+		
Wager et al. (2009b)	Heart rate	+							
Gianaros et al. (2004)	Cardio acceleration	+		-					
Gianaros et al. (2005a)*	MAP	+	+		+			+	
Gianaros et al. (2005b)*	SBP				+			+	
Gianaros et al. (2007)	SBP		+		+			+	
Gianaros et al. (2008)	MAP		+	+	+			+	
Gianaros et al. (2011)	Baroreflex suppression	+	+	+	+			+	
<i>Cortisol responses</i>									
Wang et al. (2005)	Cortisol	+			+				
Eisenberger et al. (2007)	Cortisol	+				+		+	
Pruessner et al. (2008)	Cortisol				-				
Kern et al. (2008)	Cortisol				±				
Dedovic et al. (2009)	Cortisol						+		
<i>Inflammatory responses</i>									
Slavich et al. (2010b)	TNF-alpha	+							+

Note. +, regions that were positively correlated with stressor-evoked physiology; -, regions that were negatively correlated with stressor-evoked physiology; *, data are from the same subjects using the same task, but are analyzed differently or examine two different physiological measures; MAP = mean arterial pressure; SBP = systolic blood pressure; dACC = dorsal anterior cingulate cortex; AI = anterior insula; MPFC = medial prefrontal cortex; DMPFC = dorsomedial prefrontal cortex; pACC = perigenual anterior cingulate cortex; PCC = posterior cingulate cortex; VMPFC = ventromedial prefrontal cortex.

between VMPFC and the amygdala may be one mechanism by which VMPFC activity leads to decreased threat perception and lower physiological stress responses (Delgado, Olsson, & Phelps, 2006; Eisenberger & Cole, 2012). Furthermore, studies of psychological stress show that low-stress (versus high stress) conditions are associated with greater VMPFC activity (e.g., Pruessner et al., 2008), and studies of physical pain show that low pain trials (versus high pain trials) are related to greater VMPFC activity (e.g., Atlas, Bolger, Lindquist, & Wager, 2010). Moreover, a recent study showed that VMPFC was active during the viewing of a social support figure while experiencing pain and that greater VMPFC activity was associated with greater reductions in threat-related neural activity (in dACC), again suggesting that VMPFC inhibits threat-related responding in the context of safety (Eisenberger et al., 2011a). Thus, in studies linking neural activity to physiology, activity in safety-related neural regions such as VMPFC is expected to be negatively related to physiological responses.

Neural circuitry involved in self and social cognitive processing

A final neural system likely related to physiological responses to stress is the self- and social cognitive-processing system. Self-related processing refers to circumstances in which individuals reflect upon their traits, thoughts, or feelings, whereas social cognitive processing occurs when individuals think about the traits, thoughts, or feelings of others. Self-related processing is likely to be related to physiological stress responses, as increases in self-conscious emotions (e.g., shame) and decreases in self-esteem—both of which involve reflecting upon the self—are associated with heightened stress responses (Dickerson, Gruenewald, & Kemeny, 2004a; Dickerson, Kemeny, Aziz, Kim, & Fahey, 2004b; Gruenewald, Kemeny, Aziz, & Fahey, 2004). Furthermore, stressors that involve social evaluation and the presence of other people are among the most potent activators of physiological stress response systems (Bosch et al., 2009; Bowers, Bilbo, Dhabhar, & Nelson, 2008; Dickerson & Kemeny, 2004; Dickerson et al., 2004a). Individuals undergoing these stressors are likely to be thinking about the thoughts and feelings of the evaluators (e.g., “Why did she make that face?”), suggesting that social cognitive processes may relate to increased stressor-evoked physiological responsivity. As such, neural regions involved in thinking about the self and others, including the medial prefrontal cortex (MPFC) and nearby perigenual anterior cingulate cortex (pACC), the dorsomedial prefrontal cortex (DMPFC), and the posterior cingulate cortex (PCC) may be associated with increased physiological responses to stress. This may occur in part via their projections to regions important for generating SNS and HPA responses, including the amygdala and its projections to other brainstem regions as well as the hypothalamus (Ongur & Price, 2000; see Figure 1).

Across a variety of tasks and paradigms, activity in the MPFC (Brodmann Area 10), pACC, and PCC is associated with thinking about the self (Krienen, Tu, & Buckner, 2010; Lieberman, 2007; Murray, Schaer, & Debbane, 2012). In the context of stress, activity in these regions may reflect the experience of self-conscious emotions (e.g., shame), which have previously been associated with physiological stress responses (Dickerson et al., 2004b), or the interpretation of negative, stressful information as more self-relevant (Eisenberger, Inagaki, Muscatell, Haltom, & Leary, 2011b).

Medial prefrontal cortex, pACC, DMPFC and PCC are also often active in tasks that involve thinking about the thoughts and feelings of others (Frith & Frith, 2006; Krienen et al., 2010; Lieberman, 2010; Mitchell, 2009). Thus, these regions may be especially

likely to be active during social stressors, as individuals try to understand the thoughts, feelings, and behaviors of others.

In sum, activity in neural regions that make up systems involved in processing threat (amygdala, dACC, AI), safety (VMPFC), and the self and others (MPFC, pACC, DMPFC, PCC) are expected to be associated with stressor-evoked changes in SNS and HPA activity, which may lead to increases in inflammation. With these systems in mind, we now review evidence from neuroimaging studies that have examined the neural correlates of physiological responses to stress. We focus specifically on published reports that: (1) employed a task designed to elicit a stress response from participants; (2) measured neural activity using functional MRI (fMRI), or positron emission tomography (PET); (3) included a measure of SNS, HPA, or inflammatory output; and (4) used non-patient populations (see Table 1 for a summary).

Neural Correlates of SNS-Related Activity During Stress

To date, only one known study has investigated how neural activity during a stress task is related to physiological responses in a purely sympathetic measure. This study examined how neural activity during a demanding Stroop task related to pupil diameter, a pure measure of SNS responding (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005). Results indicated that neural activity in the dACC, a core region of the threat processing system, during incorrect (relative to correct) trials of a Stroop task was related to greater pupil dilation, suggesting that the dACC may be important for stress-induced SNS activity.

The majority of research in this area has focused on the neural systems related to changes in physiological measures that are correlates of SNS-related activity, reflecting some combination of sympathetic increases and parasympathetic decreases (e.g., blood pressure, heart rate, baroreflex sensitivity). In an early study by Critchley, Corfield, Chandler, Mathias, and Dolan (2000), participants completed challenging mental arithmetic and a difficult hand-grip task, and neural activity associated with both stressful tasks was related to changes in mean arterial pressure (MAP; a weighted averaging of changes in systolic and diastolic blood pressure [SDP/DBP]) and heart rate. Neural activity in threat-related neural circuitry was related to higher blood pressure (dACC) and higher heart rate (AI) during stress, whereas activity in a safety-related neural region (VMPFC) was related to lower blood pressure.

Another study on the neural correlates of heart rate responses to stress examined how neural activity during a demanding working memory task was related to the low-frequency band of heart rate variability (LF-HRV; Critchley et al., 2003), which is thought to represent a combination of SNS activation and PNS withdrawal. Once again, neural activity in threat-related neural regions (i.e., dACC and AI) was positively associated with increases in LF-HRV.

More recently, a number of studies have examined how neural activity during stress relates to blood pressure reactivity (for a quantitative review, see Gianaros & Sheu, 2009). These studies all employed a modified Stroop color-word interference task as a form of psychological stress. Importantly, performance on incongruent trials of the Stroop was fixed so that correct responses were given on only 60% of trials, perhaps contributing to the already stressful nature of having to inhibit a pre-potent response. In addition to measuring neural activation to the stressful task, measures of blood pressure (SBP or MAP) were taken. In all four studies, neural activity in a region of the self/social cognition network (PCC) was related to greater stressor-evoked increases in blood pressure. Neural

activity in other regions of the self and social cognitive processing system (pACC, MPFC) and in threat-related neural regions (dACC, AI, amygdala) was associated with greater increases in blood pressure in some, but not all, studies (Gianaros et al., 2005a, 2007, 2008). Thus, activation in neural regions involved with thinking about the self and others, and in regions involved with processing threat, was related to increases in blood pressure.

In another set of recent studies, participants performed a speech preparation task in which they were told they would have to mentally prepare to give a speech that they would subsequently deliver to a panel of experts (Wager et al., 2009a,b). Subjects were scanned using fMRI while they prepared for the speech, as well as during a baseline period before and after the speech prep. Measurements of heart rate were taken throughout the scan. The authors examined which neural regions mediated the relation between speech preparation stress and changes in heart rate. In one study, neural activity in a threat-related neural region (dACC) mediated the relationship between social threat and heart rate increases (Wager et al., 2009a), while activity in a region implicated in thinking about the self and others (pACC) was a mediator of the stress-heart rate increase in another study (Wager et al., 2009b). Finally, in both studies, the extent of activity in VMPFC, a safety-related neural region, was negatively related to heart rate, suggesting that participants who showed greater VMPFC activity during stress exhibited less of an increase in heart rate.

To date, only one study has examined the neural correlates of baroreflex suppression,¹ another index of increased cardiovascular arousal (Gianaros et al., 2011). In this study, participants completed a task similar to the Stroop task, and accuracy was fixed so that 40% of the time, participants received negative feedback indicating they had answered incorrectly. The task was completed twice: once during an fMRI scan, and once in a separate session during which beat-to-beat blood pressure and interbeat intervals were measured to form an index of baroreflex sensitivity. Greater suppression of the baroreflex (indicative of greater sympathetic arousal) was associated with heightened neural activation in a number of brain regions, including threat processing regions (dACC, AI, amygdala), and regions involved in thinking about the self and others (MPFC, pACC, PCC). Thus, activity in threat processing and self/other processing neural systems during stress was related to greater suppression of the baroreflex and thus greater sympathetic activity.

In sum, increases in neural activity in threat-related brain regions (dACC, AI, amygdala) in response to stress are associated with subsequent increases in SNS-related activity. This pattern of activation makes sense given that these regions are part of a threat processing neural system, and increased perception of threat is associated with increased physiological responses. In contrast, relatively greater activity in a safety-related neural region (i.e., VMPFC) is associated with relatively less of an increase in SNS activity, suggesting that greater perceptions of safety during stress may be associated with lower SNS responses. A number of studies have also found that neural activity in MPFC/pACC and PCC is associated with increases in SNS reactivity. These brain regions are part of a neural system involved in thinking about the self and others, suggesting that to the extent that individuals are thinking about themselves or others during a stressor (e.g., worrying about how they are perceived, or what others are thinking), they may show greater increases in SNS responses. Given that many of the SNS measures used in neuroimaging studies are not “pure” measures of sympathetic activity, future research should incorporate more direct measures of SNS activation to specify the relation between neural activity and purely sympathetic measures.

Neural Correlates of Cortisol Responses to Stress

A handful of studies have examined how cortisol responses are related to neural activity during stress (Dedovic et al., 2009; Eisenberger, Taylor, Gable, Hilmert, & Lieberman, 2007; Kern et al., 2008; Pruessner et al., 2008; Wang et al., 2005, 2007). The first set of studies to examine this issue had participants perform difficult math problems in an MRI scanner while being prompted to go faster and to start over if an error occurred (Wang et al., 2005, 2007). Results from this study indicated that greater neural activity in a region involved in self processing and thinking about others (MPFC) was associated with greater cortisol production across the session. Interestingly, results also indicated that during a rest period following the stress task, greater activity in dACC, a threat-related neural region, was associated with greater increases in cortisol, suggesting the possibility that individuals who continue to experience some degree of threat following a stressor show a greater increase in cortisol. In a companion paper that examined gender differences in these responses, analyses revealed that, particularly for women, dACC activity following the stressor was associated with greater cortisol responses (Wang et al., 2007).

Another pair of studies compared the neural activity of individuals who showed a cortisol increase to a stressor (i.e., “responders”) to neural activity of individuals who did not show a cortisol increase (i.e., “non-responders”; Dedovic et al., 2009; Pruessner et al., 2008). In these studies, in addition to performing difficult mental arithmetic, participants were given multiple forms of negative social feedback: they were told they were performing worse than the average participant, and the experimenter told participants they needed to perform better or their data would be useless. Results from one study using these procedures indicated that the neural activity that distinguished cortisol responders from non-responders was in the DMPFC, a region often associated with thinking about the thoughts and feelings of others (Dedovic et al., 2009). In other words, individuals who showed a cortisol response to the stress task showed greater activity in this core region for understanding the behavior of others. A second study revealed that cortisol responders showed *less* activity in a safety-related neural region (VMPFC), and less activity in regions involved in thinking about the self (pACC/MPFC), compared with non-responders (Pruessner et al., 2008).

Another study on this topic had participants complete two versions of a speech and math task. In the stress condition, participants gave a speech and did mental arithmetic in front of a panel of evaluators, while in the no-stress condition, they completed these tasks alone (Kern et al., 2008). Neural activity was measured using PET following both conditions, and correlated with the extent of cortisol response during the stress condition. Results indicated that greater activity in self and social cognitive processing brain regions (MPFC, DMPFC) was related to less of a cortisol response to the stressor, while activity in a different sub-region of MPFC/pACC was positively related to cortisol responses. Thus, findings were mixed regarding the precise role of the self and social cognition neural systems in cortisol responses to stress, with distinct regions within this system correlating in opposite directions.

In a final study to investigate the neural correlates of cortisol responses to stress, participants underwent an fMRI scan while they experienced an episode of social rejection likely involving elements of social evaluation, which was elicited using a virtual ball-tossing game (i.e., Cyberball; Eisenberger et al., 2007). In a separate session, participants completed the Trier Social Stress Test (TSST) and cortisol responses to this social evaluative stressor were taken throughout the session. Greater cortisol responses to the TSST

were associated with greater neural activity in dACC, DMPFC, and PCC during social rejection. These findings suggest that, to the extent that individuals engaged neural circuitry associated with threat processing and thinking about others during an episode of social rejection, they also showed greater cortisol responses to a social-evaluative stressor.

In sum, only a handful of studies to date have investigated the neural correlates of cortisol responses to stress. In reviewing this literature, we found that data linking neural activity in brain regions often associated with self and social cognitive processing and cortisol are mixed, with some studies finding activity in these regions positively correlated with cortisol production, and other studies finding negative correlations. We also found evidence that greater neural activity in the dACC, a threat-related neural region, is associated with heightened cortisol responses. There is also initial evidence linking activity in a safety-related neural region (i.e., VMPFC) with decreased cortisol responses.

Neural Correlates of Inflammatory Responses to Stress

Only one study to date has investigated the neural correlates of inflammatory responses to stress (Slavich, Way, Eisenberger, & Taylor, 2010b). In this study, participants were scanned using fMRI while they experienced an episode of social rejection. In a separate session, participants underwent a social evaluative stressor while levels of pro-inflammatory cytokines were measured (i.e., soluble receptor for tumor necrosis factor- α , interleukin-6). Greater neural activity in threat-related neural regions (dACC, AI) and in one region of the self/social cognition system (PCC) during social rejection was associated with greater inflammatory responses to the social stressor. Although suggestive, more research is needed before we are able to fully understand the neural systems involved in inflammatory responses to stress.

Conclusions

Understanding the brain regions that are related to physiological responses to stress is an important undertaking, and a growing body of literature is now beginning to link neural activity during a stressor with stressor-evoked changes in physiology. In numerous studies, neural activity in threat-related brain regions, including the dACC, AI, and amygdala, is linked with physiological responses in SNS, HPA, and inflammatory systems. Given that the identification and experience of threat is a key feature of psychological stressors, it makes sense that activity in these regions would be linked with heightened physiological responses. However, many interesting questions regarding the role of threat-related neural systems and physiological outcomes remain to be answered.

One particularly intriguing question is the specificity of the relationship between dACC activity and physiological stress responses. Many different types of stress tasks, including those that are cognitive (e.g., performing a difficult working memory task) and social (e.g., being rejected), elicit dACC activity that is related to physiological activation. Thus, at this point it appears that many different types of stressors lead to dACC-physiological correlations. One plausible interpretation of this lack of specificity is that many tasks that we typically think of as purely “cognitive” may invoke more feelings of performance anxiety and/or implicit social evaluation than we might expect. Another possible interpretation is that the dACC responds to tasks in which relevant goals are being challenged, regardless of whether those goals are cognitive or social. It will be interesting for future research to investigate how the brain and body respond to stressors with different

psychological characteristics and to begin to disentangle the distinct neurocognitive processes engaged during different types of stress.

In addition to threat-related neural activity, physiological responses to stress have also been linked with activity in safety-related neural regions, especially the VMPFC. In this case, more VMPFC activity is typically associated with blunted physiological responses, suggesting the possibility that greater perceptions of safety or security during stress are associated with less physiological reactivity. Once again, there are exciting avenues for future research investigating the role of VMPFC in physiological stress responses: For example, how do individual differences influence the likelihood that people will show VMPFC activity during a stressor? Behavioral research suggests that a variety of social and personality factors, including trait and state experiences of social support (Uchino, 2006), optimism (Brydon, Walker, Wawrzyniak, Chart, & Steptoe, 2009), feelings of personal control or mastery (Roepke & Grant, 2011), and high self-esteem (Taylor, Lerner, Sherman, Sage, & McDowell, 2003) may buffer physiological stress responses, perhaps via increasing perceptions of safety and security during stress. Thus, a novel hypothesis would be that these and other psychosocial resources are related to greater VMPFC activity during stress (e.g., Eisenberger et al., 2011a,b), which may be involved in inhibiting physiological stress responses. Much more research is needed on how individual differences moderate the relation between neural activity and physiological stress responses in an effort to understand who may be most at risk for the health-damaging effects of stress.

Finally, neural activity in brain regions often active in tasks that involve self-reflection (MPFC, pACC, PCC) and thinking about the thoughts and feelings of others (MPFC, DMPFC, PCC) are linked with heightened physiological stress responses, though the data here are more mixed. There are exciting opportunities for future research in this area. For example, one reason why MPFC may be linked with physiological responses to stress is because MPFC activity may be associated with increased self-conscious emotions. Future studies could aim to address this hypothesis directly by explicitly eliciting self-conscious emotions in the scanner and measuring changes in SNS, HPA, and inflammatory measures. Future research could also test whether activity in social cognitive-related brain regions (MPFC, DMPFC, PCC) during stress is related to greater feelings of evaluation and attention to the thoughts of the evaluators by manipulating whether participants are attending to the evaluators and examining both neural and physiological responses. Although the precise role of self related and social cognitive-related neural activity in predicting physiological stress responses is still unclear, this is an exciting avenue for future research.

As reflected in the wizardly wisdom at the beginning of this paper, though psychological stress may often “all be in our heads”, it can still have very real effects on physiology, and ultimately, health. Initial evidence suggests that neural regions implicated in processing threat, safety, and the self and others are related to physiological responses to stress. However, much more research is needed to fully understand these relationships. It is an exciting time, as the “black box” of the brain can now be opened and we can begin to identify the neurocognitive processes that translate stressful situations into physiological changes that are relevant for health.

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Short Biographies

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Endnotes

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¹ Under non-stressful conditions, increases in blood pressure are typically associated with decreases in heart rate, and this inverse relationship is mediated by a set of specialized neurons called baroreceptors. Baroreceptors, which respond to increases in blood pressure, increase their firing rate to initiate decelerations in heart rate, a phenomenon known as the baroreflex (Dampney, 1994). Under conditions of stress, the baroreflex is suppressed, thus unlinking the inverse relationship between blood pressure and heart rate and allowing for simultaneous rises in both (Gianaros, Onyewuenyi, Sheu, Christie, & Critchley, 2011).

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