Life stress can be a gateway to ill health among vulnerable individuals. This stress-related vulnerability is determined by genetic, biobehavioral, and environmental factors that interact over the lifespan to influence individual risk trajectories. Broadly stated, human neuroimaging technology makes available methodological approaches and conceptual frameworks that enable researchers to explicate the neurobiological pathways by which stress-related processes affect health and well-being throughout life. This chapter highlights some of these approaches and frameworks for stress researchers with limited backgrounds in neuroscience, neuroanatomy, and neuroimaging. It focuses specifically on functional and structural aspects of the human brain that relate to the regulation of behavioral and peripheral physiologic response systems that are influenced by short-term (acute) and long-term (chronic) stress processes. To acquaint the reader with basic concepts in the field, we provide a general overview of the most common functional and structural neuroimaging modalities. We also consider how these modalities can be used to answer questions about stress-related neural processes, particularly within the context of their relevance to health. We then summarize experimental design and inferential issues relevant to executing and interpreting neuroimaging studies. Afterward, we provide a concluding overview of neuroimaging studies of specific brain systems that play a dual role in processing stress-related information and regulating biobehavioral stress responses.

**OVERVIEW OF NEUROIMAGING MODALITIES AND METHODS**

Not all neuroimaging modalities and methods are well suited to addressing every question about stress processes. This is particularly true for questions about the relationships between stress-related neuroimaging variables and markers of health status and risk. Furthermore, as readers of this volume are aware, operational definitions of “stress” vary between investigators from different disciplinary backgrounds (Cohen, Kessler, & Underwood-Gordon, 1997; Eichler, Silverman, & Pratt, 1986). Consequently, varied stress definitions will necessarily influence the particular neuroimaging variables that are measured and the stress-related pathways to health that are emphasized in a given study. Importantly, stress-related processes can be conceptualized and measured at multiple levels of analysis, over multiple time scales, and throughout multiple stages of life in different populations (Monroe, 2008). We adopt the conceptual perspective that stress reflects a transactional process arising from real or perceived environmental demands that are appraised in relation to the adaptive coping resources of an individual (Holroyd & Lazarus, 1982; Lazarus & Folkman, 1984; see Smith, this volume). We also focus on studies of stress processes measured at the level of brain function and structure among otherwise healthy adults. By extension, we assume that the biological, behavioral, and interpersonal responses that ensue from stress perception and appraisal processes may influence risk for and resilience against ill health (Cohen et al., 1997; Lovallo, 2005a). Critically, we emphasize that the brain is a central mediator of these stress regulatory processes, insofar as distributed brain networks encode, filter, and store environmental information according to unique personal histories and life experiences to determine what is “stressful” to the individual (McEwen, 2007; Dallman, this volume). Furthermore, we emphasize that the brain is a central target of stress processes, insofar as stressful experiences can affect brain morphology and functional plasticity through interacting feedforward and feedback mechanisms expressed between the central and peripheral nervous systems (McEwen, 2007).

With these points in mind, we suggest that functional neuroimaging methods are well suited in most instances to study shorter-term (acute) stress processes. For example, functional neuroimaging methods can be used to ask questions about the short-term changes in neural activity associated with (i) perceptions of acute stressors encountered inside of an imaging scanner; (ii) subjective appraisals of one’s abilities and resources to cope with the demands imposed by such stressors; and (iii) behaviors and peripheral physiologic responses that are modulated by and interact with stress perception, appraisal, and coping processes. By contrast, we suggest that structural neuroimaging methods are well suited in most instances...
to study the putative effect of longer-term (chronic) stress processes on brain morphology.

As illustrated below, however, functional and structural neuroimaging can be combined flexibly in a single study to gather multimodal evidence on aspects of the brain associated with acute and chronic stress processes. Indeed, functional neuroimaging methods could be used to study acute stressor appraisal and responding processes among populations characterized by differing histories of chronic life stress. Similarly, structural neuroimaging methods could be used to assess the relationship between brain morphology and short-term changes in functional neural activity and physiologic reactivity elicited by acute stressors.

**FUNCTIONAL NEUROIMAGING METHODS**

Several functional neuroimaging methods are available for studying stress processes, including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), single photon emission computed tomography, magnetoencephalography, and near-infrared spectroscopy. These methods have been described in detail in several recommended texts (Buxton, 2002; Cabeza & Kingstone, 2006; Frackowiak et al., 2003; Huettel, Song, & McCarthy, 2004; Jezzard, Matthews, & Smith, 2001; Toga & Mazziotta, 2002). For interested students and researchers, there are also a number of introductory workshops and training institutes on these methods that are regularly announced by the Organization for Human Brain Mapping (http://www.humanbrainmapping.org/). Because of their widespread use and availability, we review the most common functional neuroimaging methods, PET and fMRI. These two methods have advantages and disadvantages with respect to one another, and each can provide unique information about stress-related neural processes.

In general, PET and fMRI differ in their invasiveness to the individual, in their ability to localize ongoing changes in neural activity to particular brain areas (referred to as spatial resolution), and in their ability to resolve the timing of changes in neural activity in relation to a given psychological, behavioral, or physiologic process (referred to as temporal resolution). The power of both methods is that they can quantify interactions between neural activity patterns from distributed brain areas in short periods of time. In this way, PET and fMRI can reveal dynamic changes in the activity of brain networks, as opposed to isolated patterns of activity from disparate brain areas. Importantly, these functional changes in brain networks can be related to wide-ranging cognitive, emotional, behavioral, physiologic, and interpersonal processes important for understanding the neurobiological pathways linking stress and health.

We emphasize, however, that PET and fMRI methods evolve rapidly. Consequently, extensive treatments of these methods in a single chapter would be dated by the time the chapter reaches print. Therefore, we consider key issues involved in PET and fMRI research, and we refer readers to in-depth resources where relevant. Throughout, we emphasize the use of PET and fMRI for indirectly measuring regional increases and decreases in brain activity, conventionally referred to as patterns of brain “activation” and “deactivation,” which are complexly determined by changes in brain blood flow, oxygen concentration, and metabolism in areas of neural activity.

**POSITRON EMISSION TOMOGRAPHY**

Both PET and fMRI quantify regional changes in hemodynamic and metabolic activities that are correlated with changes in neural activity (Raichle, 1998, 2006; Savoy, 2001). Neuroimaging methods using PET provide three-dimensional images of the brain that correspond to quantitative levels of glucose metabolism, oxygen consumption, regional cerebral blood flow, and neurotransmitter receptor-binding potentials during passive (e.g., resting) or active (e.g., task-related) behavioral states. This is done by localizing the emission of positrons from radioactive tracers injected into the bloodstream. With PET, these tracers can be distributed and concentrated differentially throughout the blood vessels supplying brain tissue. In general, PET methods capitalize on these distributional and concentration characteristics to assess levels of brain activity because of the close relationships between cellular (neural) activity, blood flow, and metabolism. The most common PET methods rely on 18-fluorodeoxyglucose ("FDG) and hydrogen-2 oxygen-15 (H$_2$ ["O]) as injected tracers to measure regional cerebral glucose metabolism and cerebral blood flow, respectively. To localize brain activity patterns, PET data are analyzed using kinetic modeling procedures that estimate the spatial concentration of a particular radioactive tracer. The resulting PET images can then be examined within individuals across experimental periods or between individuals at rest or during task performance as a function of another variable of interest (e.g., as a function of stressor-evoked changes in a measure of peripheral physiologic reactivity). For example, changes in heart rate, blood pressure, heart rate variability, and cortisol (peripheral measures often used in stress science) have been linked to regional cerebral blood flow patterns using PET imaging (Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Gianaros, Van Der Veen, & Jennings, 2004; Lane, Reiman, Ahern, & Thayer, 2001; Pruessner et al., 2007).

**FUNCTIONAL MAGNETIC RESONANCE IMAGING**

The biophysical basis of fMRI differs from PET in several ways. With fMRI, short-term changes in neural activity (e.g., on the order of seconds) can be localized without...
ionizing radiation or radioactive tracers. Specifically, fMRI localizes neural activity by exploiting the blood oxygenation level–dependent (BOLD) effect, a phenomenon discovered in nuclear magnetic resonance physics (Ogawa, Lee, Kay, & Tank, 1990; Ogawa, Lee, Nayak, & Glynn, 1990; for review, see Raichle, 2006). The BOLD effect is based on the concentration of oxygen in the blood that flows to brain areas in which there is a change in neural activity. More precisely, when the activity of neural tissue increases, blood flow to that tissue will increase to provide a metabolic substrate for cellular activity (Buxton, 2002; Huettel et al., 2004; Logothetis, 2002). However, in areas of neural activity, blood flow will change out of proportion to oxygen consumption. As a result, there is a change in the oxygen concentration within blood vessels supplying that tissue. This change in oxygen concentration can be detected with magnetic resonance imaging (MRI) because the oxygen level in hemoglobin (the protein molecule in red blood cells) changes the extent to which hemoglobin disturbs a local magnetic field. Hence, changes in fMRI BOLD signal intensity reflect changes in the ratio of deoxygenated to oxygenated hemoglobin in the blood supplying particular brain areas. Given that the BOLD effect is dependent on measuring relative changes in oxygen concentration, fMRI studies routinely use task paradigms involving a comparison of brain activity during two or more conditions. These comparisons are then used to quantify relative functional neural changes, which have been labeled as patterns of BOLD “activation” and “deactivation.”

From a methodological perspective, it is important to emphasize that the fMRI BOLD signal is subject to many confounding factors, including the dramatic effects of even slight (millimeter) head movements, the compromising effect of cerebrovascular insults on the blood vessels supplying brain tissue, the appreciable decrease in the signal-to-noise ratio in particular areas of the brain that abut air–tissue interfaces (i.e., sinus areas near the ventral orbitofrontal cortex), and the physical movement of the brain that occurs with each breath and heartbeat. Furthermore, one disadvantage of fMRI relative to PET is that it poses challenges to recording concurrent changes in peripheral physiology, which is often a major goal in stress research. This disadvantage stems from several sources. One includes the radiofrequency and electrical artifacts introduced into peripheral recordings (e.g., the electrocardiogram) by the changing magnetic gradients imposed by fMRI scanning. Another disadvantage is that the metallic instrumentation often used for peripheral physiologic recording is not safe in the MRI environment (http://www.mrisafety.com/). However, instrumentation for recording peripheral physiology in the MRI environment is becoming increasingly available, and this instrumentation will better allow for the assessment of electroencephalographic, electrocardiographic, blood pressure, respiratory, and skin conductance measures during fMRI protocols. If such instrumentation is not available to the researcher, then an alternative approach to integrating assessments of peripheral physiology into fMRI stress studies is to have participants perform the same stressor task in an fMRI scanner and in a laboratory setting (or even in a plastic replica of the scanner to emulate the same experimental environment [e.g., laying in the same position within a confined space while being exposed to loud, ∼90 dB, noise]).

Notwithstanding these issues, fMRI has several advantages over PET, including the ability to scan the same person over multiple sessions within a short period of time (because of the lack of radiation exposure), the higher spatial and temporal resolution of the BOLD signal, and the relatively lower cost and wider availability of fMRI at most institutions. Indeed, the increasing availability of MRI scanners with higher magnetic field strengths (measured in Tesla units, where 1 Tesla = 10,000 Gauss) will provide unprecedented opportunities for localizing functional and structural aspects of the brain with more precise spatial resolution.

**ARTERIAL SPIN LABELING**

As noted above, the fMRI BOLD signal indirectly reflects relative changes in neural activity because it reflects interacting changes in neurovascular function and oxygen concentration. In this way, measuring the BOLD signal has at least one disadvantage with respect to PET; namely, it provides a surrogate estimate of neurophysiologic activity. However, by using specialized MRI scanning parameters (referred to as pulse sequences), the quantitative parameter, regional cerebral blood flow, can be estimated with MRI methodology by a technique called perfusion imaging (Detre & Wang, 2002). This technique is gaining increasing use in the field, and it has been applied in neuroimaging studies of stress processes by Wang et al. (2005, 2007). Hence, perfusion MRI is an emerging noninvasive technique that may better capture quantitative changes in regional cerebral blood flow that are more closely related to neural activity and metabolism patterns relevant to stress processes.

**STRUCTURAL NEUROIMAGING METHODS**

In the following, we focus mainly on functional neuroimaging studies of stress processes. However, as part of PET and fMRI scanning protocols, researchers often collect high-resolution structural images of the brain. For functional neuroimaging studies, structural images are often used to localize changes in brain activity to a single person’s unique brain morphology. This is done by co-registering functional and structural brain images before statistical analysis (Buxton, 2002; Huettel et al., 2004). An added data preprocessing step discussed below is to co-register both structural and functional brain images from a single individual to a standardized brain
template or coordinate system, which is referred to as spatial normalization.

In addition to these purposes, high-resolution structural images also provide detailed information about gray and white matter brain tissue that can be analyzed to assess quantitative aspects of brain morphology, including the volume of gray and white matter tissue in different brain areas, the thickness of the cortex across the brain, and the integrity and projections of major white matter fiber tracts. In this way, structural neuroimaging methods can be useful for assessing stress-related variables in association with individual differences in brain morphology. Below, we provide examples of structural neuroimaging methods that have been used in studies of chronic life stress and work examining cardiovascular and neuroendocrine reactivity to acute stressors.

BASIC PRINCIPLES OF FUNCTIONAL NEUROIMAGING STUDY DESIGN AND INFERENCE

In most functional neuroimaging studies, one of the goals is to characterize relative changes in neural activity in specific brain areas when a person performs a behavioral task. A longstanding supposition is that achieving this goal will help explicate the specific brain areas involved in mediating cognitive, emotional, and behavioral processes (Raichle, 1998, 2006; Savoy, 2001). For most PET and fMRI studies, this goal is achieved with a canonical “subtraction paradigm,” derived from the work of the cognitive scientist, Donders (1969). Using this paradigm in functional neuroimaging studies involves requiring people to engage in a behavioral task with two or more conditions. One (or more) of the conditions will serve as an active condition of interest, whereas another (or more) will serve as a control condition. In a common approach to the analysis of the neuroimaging data, brain “activation” will be determined by subtracting the control condition from the active condition to compute a so-called “contrast” or “difference” image of neural activity.

For example, an active “stressful” task may require a person to read words reminding her or him of a previous traumatic experience. We are not interested in brain areas engaged by reading words per se. Hence, in a hypothetical control condition, we would require the person to read words that are emotionally neutral and not related to the traumatic experience. With this design, we would determine brain “activation” by subtracting BOLD or PET images of the control condition from those of the active condition to reveal brain activity specifically increased by processing trauma-related words. The assumption here is that brain activity common to word reading in both conditions would be cancelled out by the subtraction procedure.

In addition to assessing “activation,” patterns of “deactivation” could also be assessed by subtracting BOLD or PET images of the active (presumptively “stressful”) condition from those of the control (“neutral”) condition to reveal brain areas in which there were relative decreases in neural activity during the trauma word reading condition. Although the logic supporting the subtraction paradigm has been questioned for years, variants of the subtraction paradigm remain dominant in functional neuroimaging studies (Raichle, 1998, 2006; Savoy, 2001).

Importantly, there are a range of experimental designs in which the subtraction paradigm can be implemented. The most common are blocked and event-related designs (Aguirre & D’Esposito, 2000; Culham, 2006; Donaldson & Buckner, 2001; Rosen, Buckner, & Dale, 1998). In a typical blocked design, two or more task conditions are alternated in blocks or epochs for predefined time periods (e.g., ~15 seconds to ~2 minutes, depending on the neuroimaging modality). For each alternating block, only one task condition is administered. According to the subtraction paradigm logic described above, if the task conditions in a blocked design differ only in the process of interest that are engaged (e.g., processing trauma vs. nontrauma words), then the fMRI or PET signal changes in particular brain areas that differentiate the conditions will presumably reveal patterns of neural activity associated with the process of interest.

Although blocked designs are common, one of their disadvantages is that they present challenges to assessing short-term changes in neural activity (e.g., those occurring within a few seconds after a stimulus is presented or after a behavioral response is made). This has led to the development of event-related designs, particularly in fMRI research (at this time, the temporal resolution in PET imaging is insufficient for event-related designs). In event-related fMRI designs, aspects of brief changes in the BOLD signal can be quantified just before or just after a single stimulus (e.g., the presentation of a word or picture) or a behavioral response (e.g., a behavioral error or a correct response during task performance). In this way, short-term changes in the BOLD signal waveform relative to (subtracted) “control” levels can be assessed and associated with individual difference factors or stimulus or response variables (Donaldson & Buckner, 2001; Rosen et al., 1998). Importantly, these short-term changes in the BOLD signal can reveal considerably more information than the aggregate difference in neural activity between two or more conditions, as determined in blocked designs. However, it is also important to note that fMRI BOLD signal changes are small in comparison with the noise inherent to the signal, resulting in reduced statistical power for event-related designs (Donaldson & Buckner, 2001). Hence, an increasing number of fMRI studies use mixed designs that blend both blocked and event-related features (Mechelli, Henson, Price, & Friston, 2003; Visscher et al., 2003).
RESTING STATE ACTIVITY

In addition to assessing task-related changes in neural activity with blocked and event-related designs, there has been a recent increase in research on the so-called “resting state” patterns of neural activity (for review, see Buckner, Andrews-Hanna, & Schacter, 2008). These resting state patterns can refer to the basal metabolic rate, blood flow, and even statistical correlations (connectivity patterns) expressed within and between different brain areas in an unchallenged (resting) period. Importantly, different brain areas may express different levels of metabolic activity and blood flow in the absence of performing any task, and these metabolic differences can vary as a function of individual differences in a given parameter of interest. For example, Wang et al. (2005) used perfusion fMRI to show that resting blood flow to the anterior cingulate cortex and other areas of the prefrontal lobe was associated with heart rate and cortisol reactions to a subsequent mental arithmetic stressor. This particular finding underscores the important role of resting patterns of brain activity in predicting individual differences in stress reactivity. However, the psychological meaning of these resting state patterns of brain activity in relation to patterns of stress reactivity and health status remains to be determined.

In addition to patterns of resting metabolism and blood flow illustrated above, there has been growing interest in characterizing the statistical correlations between spontaneous fluctuations in resting activity in brain areas that are anatomically networked to one another. This approach has yielded important information about the functionally relevant correlations between activity in brain areas comprising broader regulatory neural circuitries, which may be compromised among individuals with and vulnerable to stress-related psychiatric syndromes, including major depressive disorder (Greicius et al., 2007; Greicius, Krasnow, Reiss, & Menon, 2003; Greicius, Supekar, Menon, & Dougherty, in press). Following conventional nomenclature, statistical correlations between concurrent or time-lagged changes in neural activity (e.g., time-varying oscillations in the fMRI BOLD signal) are referred to as patterns of connectivity (Friston, 1994; Horwitz, 2003; Ramnani, Behrens, Penny, & Matthews, 2004).

INFERENTIAL ISSUES

As discussed earlier, neuroimaging methods offer several approaches to studying patterns of brain activity of interest to stress researchers. Unfortunately, however, there are no universally agreed upon ways to design, analyze, and interpret all types of functional and structural neuroimaging studies. Nevertheless, there are some standards of practice that should be considered. First, when possible, neuroimaging studies should be driven by focused hypotheses targeting specific brain areas or networks of interest. This focus could be based on previous animal or human research on the processes presumably supported by the brain area(s) of interest. Questions like “Where in the brain does activity change when people are under stress?” are unlikely to move the field forward in a measurable way. Rather, more focused questions like “Does increased or decreased activity in the hippocampus, which regulates the hypothalamic-pituitary–adrenal (HPA) axis, correlate with changes in the release of the stress hormone, cortisol, when people engage in social stressor task?” (cf., Pruessner et al., 2007) are better suited to defining the neurobiological pathways by which stress processes relate to physical and mental health. Second, careful attempts should be made to control for salient confounders in functional and structural neuroimaging studies. For functional neuroimaging studies of task-related changes in brain activity, this often involves matching control and active conditions of interest along as many stimulus and response dimensions as possible. Importantly, this will support stronger inferences using the subtraction procedure described above. Such control could involve matching conditions (e.g., stressor and nonstressor conditions) in terms of the number of motor responses that are made during task performance, the perceptual and cognitive aspects of the stimuli presented, and the peripheral physiologic recording procedures if they are used (e.g., inflating a blood pressure cuff during both control [nonstress] and active [stress] conditions). Again, it is important to remember that any difference between two conditions in a neuroimaging study will likely be reflected in patterns of brain activity revealed by the subtraction paradigm, only some of which are of interest to the researcher. Other inferential issues in functional neuroimaging research have been detailed elsewhere (Logothetis, 2008; Sarter, Berntson, & Cacioppo, 1996).

Furthermore, for both functional and structural neuroimaging studies of individual differences, it is critical to account for factors that could affect between-person variation in brain activity or morphology. These sources of variation may include patient or health status, age, gender, cognitive functioning, and other factors. For example, when comparing two groups (e.g., those who do and do not report previous exposure to major stressful life events) in terms of their functional neural activation to a stressor, a global difference between the groups in intellectual ability may influence task comprehension and performance, resulting in a confounded group difference in stressor-related brain activation. Furthermore, factors such as age and gender are associated not only with aspects of brain morphology (Coffey et al., 1998; Gur, Cunning-Dixon, Turetsky, Bilker, & Gur, 2002; Raz et al., 1997, 2005) but also with aspects of brain activation under certain stressor task conditions (Wang et al., 2007). Thus, accounting for potentially confounding individual difference factors is critical.
Finally, for functional neuroimaging studies, there are a number of statistical procedures available for (i) making simple comparisons between task conditions or event types; (ii) assessing neural activity patterns that vary according to interactions between task conditions and events; and (iii) computing correlations between changes in neural activity to determine connectivity patterns expressed between brain areas. Similarly, for structural neuroimaging studies, there are an equally large number of statistical procedures to assess aspects of brain morphology in association with individual difference factors. For all of these procedures, it is important to account for the inflated likelihood of observing statistically significant effects by chance alone, given that (i) the brain is a three-dimensional structure necessitating multiple (often mass univariate) statistical tests and (ii) multiple correlated measures are often derived from repeated observations of the same person over time, as in the case of functional neuroimaging studies and longitudinal structural neuroimaging studies (Genovese, Lazar, & Nichols, 2002; Nichols & Hayasaka, 2003). Hence, it is routine to use random- or mixed-effects statistical analyses to permit appropriate generalizations to the population and to apply corrections for performing multiple statistical tests across the brain (Friston et al., 1995; Worsley, Evans, Marrett, & Neelin, 1992).

APPLICATIONS OF NEUROIMAGING METHODS IN STRESS RESEARCH

We now consider recent functional and structural neuroimaging studies of stress processes. Brain areas in these studies can be referenced both by conventional neuroanatomical labels and by their spatial location in standard three-dimensional coordinate systems. For these coordinate systems, it is assumed that an individual's brain has been co-registered (also called normalized) to a standard anatomical template. The most common of these are the Talairach and Tournoux and Montreal Neurological Institute template coordinate systems (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Within these coordinate systems, anatomical areas or coordinates are defined and reported with respect to their distance in millimeters from two major white matter fiber tracts, the anterior and posterior commissures.

As a general orientation, spatial coordinates for different brain areas are reported along three planes, as illustrated for the amygdala in Figure 39.1. These planes are usually referred to as sagittal, coronal, and horizontal (or axial). In humans, the sagittal plane cuts the brain along its midline, from left to right. The coronal plane cuts the brain from front (anterior, also called rostral) to back (posterior, also called caudal). The horizontal plane runs parallel to the ground and cuts the brain from top (superior, also called dorsal) to bottom (inferior, also called ventral). By using these planes, anatomical coordinates localizing brain areas are reported in x, y, and z values. X values locate areas along the sagittal plane, such that positive values are in the right hemisphere and negative values are in the left hemisphere; y values locate areas along the coronal plane, such that positive values are anterior (rostral) and negative values are posterior (caudal); and z values locate areas along the horizontal (axial) plane, such that positive values are superior (dorsal) and negative values are inferior (ventral). These values can be seen in figures presented later in this chapter that depict areas of brain activation.

FUNCTIONAL NEUROIMAGING STUDIES OF STRESS PROCESSES

To organize the rapidly expanding neuroimaging literature on stress, it may be helpful to categorize studies according to whether they investigate acute, chronic, or some combination of acute and chronic stress processes. This scheme may be particularly helpful in determining which topical questions about stress processes have yet to be addressed with neuroimaging. To this end, neuroimaging studies of stress may be categorized in the following way. Some have used acute stressor tasks administered inside of an imaging scanner (hereafter called a “scanner stressor”) to study short-term stress processes, such as acute stressor-evoked neural or peripheral physiologic reactivity. Others have used neuroimaging designs comparing individuals or groups of individuals defined according to a person's characteristic, possibly reflecting an aspect of chronic or ongoing life stress. Furthermore, both acute scanner stressors and chronic stressor groups may be categorized as falling into physical, mental, emotional, or social domains. The following list of “scanner stressors” used to evoke short-
term changes in stress reactivity in the recent literature is not exhaustive but illustrates this domain-related categorization scheme. Examples of physical stressors include breath holding, yohimbine administration, malodors, and pain (Cameron, Zubieta, Grunhaus, & Minoshima, 2000; Kastrup, Li, Glover, & Moseley, 1999; Schifman & Williams, 2005; Scott, Heitzeg, Koepe, Stohler, & Zubieta, 2006). Mental stressors include mental arithmetic with or without social evaluation (Soufer et al., 1998; Wang et al., 2005), unsolvable anagrams (Schneider et al., 1996), and variants of the Stroop color-word interference task (Gianaros, Jennings, Sheu, Derbshire, & Matthews, 2007; Gianaros, May, Siegle, & Jennings, 2005). Emotional stressors include scripts or pictures of personal stressful life events (Gündel, O'Connor, Littrell, Fort, & Lane, 2003; Sinha, Ladadie, Skudlarski, & Wexler, 2004). Social stressors include social rejection (Eisenberger, Lieberman, & Williams, 2003) or socially evaluative stress (Pruessner et al., 2008). A related set of tasks include tasks designed to measure brain activation during the reduction of stress, such as engaging in biofeedback (Critchley, Melmed, Featherstone, Mathias, & Dolan, 2001), being humored (Watson, Matthews, & Allman, 2007), and performing mindfulness meditation (Creswell, Way, Eisenberger, & Lieberman, 2007) to reduce the experience of stress.

Chronic stress has also been studied in neuroimaging studies and has most often been conceptualized as a characteristic of a person experiencing some form of background or enduring life stress that can range in length and severity along continua. Such sources of life stress could stem from functional medical disorders involving chronic pain or emotional disorders involving persistent psychological distress. Stress-related medical disorders studied with neuroimaging include chronic pain syndromes (Derbyshire, 2003; Williams & Gracely, 2006) and functional gastrointestinal disorders (Drossman, 2005; Hobson & Aziz, 2004; Ringel et al., 2008). Emotional disorders associated with life stress include posttraumatic stress disorder (Bremner, 1999; Nemeroff et al., 2006; Lanius et al., 2004; Tabe, Rauch, Lanius, & Hurley, 2003), major depression (Drevets, 1999, 2000; Phillips, Drevets, Rauch, & Lane, 2003b; Mayberg et al., 2003), clinical anxiety (social anxiety, generalized anxiety, and specific phobias) (Etkin & Wager, 2007), and complicated grief (O'Conner et al., 2008). Other sources of chronic or ongoing social or interpersonal life stress may relate to early life adversity (Bremner et al., 2003; Cohen et al., 2006; Pollak, 2005; Vythilingam et al., 2002) and low socioeconomic status (Gianaros, Horenstein et al., 2007, 2008).

**BRAIN SYSTEMS IMPORTANT FOR LINKING STRESS-RELATED PROCESSES TO HEALTH**

Much of our understanding of the brain systems that link stress-related social, psychological, behavioral, and physiologic factors to resilience and ill health over the lifespan remains incomplete. Before discussing some of the brain systems that have been most widely studied in human stress neuroimaging research, it is important to emphasize that multiple brain systems act as parallel networks to support a range of “homeostatic” and “nonhomeostatic” functions during stressor processing, which appreciably complicates our understanding of the neurobiological pathways linking stress and health (Soufer, Arrighi, & Burg, 2002). Hence, an exclusive focus on one brain area in isolation of other areas will often lead to oversimplified accounts of the mechanisms linking stress-related factors to particular health outcomes.

The key brain areas anatomically networked to one another that have been studied most often in neuroimaging stress research are referred to as limbic or paralimbic areas, which are also referred to as an integrated system. The development of the concept of a limbic system is widely attributed to Papez (1937, 1995), who described a circuit mediating emotional behaviors, such as emotional expression and feeling (Dalgleish, 2004). Building on the conception of this circuit, MacLean (1949) later modified Papez’s definition of the limbic system to include the amygdala. MacLean also suggested a critical role for limbic areas in linking the processing of emotional information to peripheral autonomic and neuroendocrine changes contributing to the pathophysiology of major syndromes of interest to stress researchers (e.g., essential hypertension). Broadly speaking, limbic areas are viewed as networked structures that coordinate behavior with neuroendocrine, autonomic, and immune functions in the service of coping adaptively with emotionally salient environmental stimuli and challenging psychosocial demands that tax an individual’s coping resources (Fuchs & Flugge, 2003; Herman, Ostrander, Mueller, & Figueiredo, 2005; Lane, Waldstein, Critchley et al., 2009; Lane, Waldstein, Jennings et al., 2009; LeDoux, 2000; Phillips, Drevets, Rauch, & Lane, 2003; Rolls, 1999).

In the following, we review neuroimaging studies focusing on a set of these anatomically networked limbic areas, including the cingulate cortex, orbital and medial prefrontal cortex, amygdala, hippocampus, nucleus accumbens and related striatal areas, and the hypothalamus. For a more comprehensive treatment and description of these systems within the context of their importance for stress and health, the reader is referred to recent reviews (Lane, Waldstein, Critchley et al., 2009; Lane, Waldstein, Jennings et al., 2009). In the following sections, we particularly focus, for illustrative purposes, on functional neuroimaging studies of acute stress-evoked cardiovascular reactivity, because it informs our understanding of the neurobiological pathways that may link stressor processing with cardiovascular reactions implicated in coronary heart disease (CHD) risk. We then review recent functional neuroimaging studies of stress-related neuroendocrine activity also relevant to health outcomes. We conclude with a brief summary of emerging functional and structural neuroimaging studies of chronic stress processes.
FUNCTIONAL NEUROIMAGING STUDIES OF ACUTE STRESSOR-EVOKED CARDIOVASCULAR REACTIVITY

Psychological stress has long been implicated in the development of CHD (Kop, 1999; Rozanski, Blumenthal, & Kaplan, 1999). There are many interacting genetic, environmental, and biobehavioral pathways by which psychological stress may promote CHD risk over the lifespan. One heavily investigated pathway is a person’s tendency to show exaggerated cardiovascular reactions to psychological stressors (Krantz & Manuck, 1984). Converging evidence indicates that exaggerated cardiovascular—specifically blood pressure—reactions to acute stressors are associated with CHD risk (Kamarck & Lovallo, 2003; Schwartz et al., 2003; Treiber et al., 2003). However, it is only recently that the neurobiological pathways linking the processing of psychological stressors to blood pressure and other forms of cardiovascular reactivity and CHD risk have begun to be studied and incorporated into integrated theoretical frameworks (Berntson et al., 1998; Lovallo, 2005b; Lovallo & Gerin, 2003). For illustration, we review stress research targeting specific paralimbic and limbic brain systems that may influence cardiovascular, specifically blood pressure, reactivity and risk for CHD.

To begin, stressor-evoked increases in blood pressure result from net changes in cardiac output and peripheral vascular resistance that are mediated by increased sympathetic nervous system activity, suppressed parasympathetic nervous system activity, and increased HPA activity (Obrist, 1981). These cardiovascular, autonomic, and neuroendocrine adjustments are believed to provide metabolic and hemodynamic support for adaptive behavior (e.g., fight-or-flight) (Cannon, 1928; McEwen, 1998; Obrist, 1981; Sapolsky, Romero, & Munch, 2000). Some individuals, however, show exaggerated increases in blood pressure and other types of cardiovascular activity that exceed the metabolic demands of a given psychological stressor (Turner, Carroll, Hanson, & Sims, 1988). These individual differences in stressor-evoked cardiovascular reactions are relatively stable response tendencies (Allen et al., 1987; Gerin, Pieper, & Pickering, 1993; Kamarck & Lovallo, 2003; Llabre, Spitzer, Saab, Ironson, & Schneiderman, 1991; Manuck, Kamarck, Kasprowicz, & Waldstein, 1995) that have been associated with risk for hypertension (Knox, Haussdorff, & Markovitz, 2002; Matthews, Salomon, Brady, & Allen, 2003; Matthews, Woodall, & Allen, 1993; Menkes et al., 1989; Ming et al., 2004), stroke (Eversen et al., 2001), and myocardial infarction (Alderman, Ooi, Madhavan, & Cohen, 1990). By extending previous epidemiologic work, recent functional and structural neuroimaging studies have begun to identify some of the brain systems that may centrally link individual differences in cardiovascular reactivity to CHD risk. Specifically, individual differences in blood pressure reactivity have been linked to patterns of activation involving several paralimbic brain areas, including the cingulate cortex, insula, and amygdala. These areas are discussed in the following sections.

CINGULATE CORTEX

The cingulate cortex forms a belt around the corpus callosum. It is broadly viewed to support cognitive, emotional, nociceptive, skeletal-motor, and visceral-motor processes. Regional differences in cellular architecture and projections to and from other brain areas define three putatively distinct functional subdivisions of the cingulate cortex, nominally labeled as (i) a rostral (perigenual) affective division; (ii) a dorsal (supragenual) cognitive motor division; and (iii) a caudal (retrosplenial) evaluative monitoring division (Bush, Luu, & Posner, 2000; Devinsky, Morrell, & Vogt, 1995; Paus, 2001; Vogt, 2005; Vogt, Finch, & Olson, 1992; Vogt, Nimchinsky, Vogt, & Hof, 1995). In addition to supporting cognitive- and emotion-related functions, cumulative evidence implicates each of these cingulate subdivisions in association with stressor-evoked blood pressure reactivity.

The perigenual anterior cingulate cortex (pACC) is believed to support several emotion- and stress-related functions, including the automatic appraisal of salient environmental and personal events, the experience of emotional states, and the regulation of behavioral and autonomic responses to emotional and stressful stimuli (Bush et al., 2000; Critchley, 2005; Paus, 2001; Phillips, Drevets, Rauch, & Lane, 2003a; Vogt, 2005). For example, neuroimaging evidence demonstrates that the pACC is engaged by mood induction procedures (Mayberg et al., 1999), by the presence of distracting emotional information during cognitive task performance (Mohanty et al., 2007), and by committing errors during cognitive tasks (Kiehl, Liddle, & Hopfinger, 2000). Complementing this work, both animal and human findings document an important role for the pACC in supporting stressor-evoked autonomic and cardiovascular reactivity. Such a role for the pACC is instantiated through its reciprocal circuitry with adjacent areas of the orbital and medial prefrontal cortex, anterior insula, amygdala, and areas in the hypothalamus, periaqueductal gray (PAG), pons, medulla, and the sympathetic intermediolateral cell column of the spinal cord (Barbas, 2000; Barbas, Saha, Rempel-Clower, & Ghoshgai, 2003; Buchanan & Powell, 1993; Critchley, 2005; Vogt, 2005). As such, the pACC—along with networked areas of the dorsal and posterior cingulate discussed next—may provide for an interface between automatic stressor appraisal processes and concurrent cardiovascular control. Supporting the view that the pACC is functionality associated with stressor-evoked blood pressure reactivity, greater stressor-evoked pACC activity across individuals has been associated with larger-magnitude blood pressure reactions to a variant of a Stroop color-word interference stressor (Gianaros et al., 2005; Gianaros, Jennings, Sheu et al., 2007; Gianaros, Sheu et al., 2008). Furthermore, there
also implicates dACC areas in emotion-related processes associated with physiologic reactivity and subjective distress. For example, dACC areas are engaged by states of pain-related anxiety (Ochsner & Gross, 2005; Vogt, Berger, & Derbyshire, 2003), intentional regulation of autonomic activity (Critchley et al., 2002), and awareness of subjective emotional experiences (Lane et al., 1998). Hence, Critchley (2005) posits that the dACC may be particularly important for generating autonomic and cardiovascular responses via projections to subcortical areas to support volitional, cognitive, and emotional behaviors. Consistent with this view, stressor-evoked blood pressure reactivity has been shown to covary with heightened dACC activation (Critchley et al., 2000; Gianaros et al., 2005).

The posterior cingulate cortex (pCC) is believed to support evaluative processes related to cognition and emotion, including (i) maintaining a general representation of the environment; (ii) gauging the emotional salience of environmental events; and (iii) monitoring the environment for threatening stimuli (Gusnard, Raichle, & Supe, 2001; Holroyd & Coles, 2002; Ridderinkhof, Crone, & Nieuwenhuis, 2004). After conflict detection, dACC areas engage prefrontal, motor, and parietal cortices to resolve conflicts and minimize behavioral error by modulating attention, working memory, and motor control processes (Paus, 2001).

Growing evidence is parallel structural neuroimaging evidence that individuals with reduced gray matter volume in the pACC also show larger-magnitude blood pressure reactions to the same stressor (Gianaros et al., 2008; Figure 39.2).

Areas in the dorsal anterior cingulate cortex (dACC) are broadly viewed as supporting processes related to attention, effortful executive control, and conflict and error monitoring. These processes are instantiated by reciprocal circuitry with the lateral prefrontal cortex, motor and supplementary motor cortex, and posterior parietal cortex (Vogt & Pandya, 1987). A conventional view is that dACC areas monitor for conflicts between competing streams of incompatible information, which foster the potential for behavioral error (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Holroyd & Coles, 2002; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). After conflict detection, dACC areas engage prefrontal, motor, and parietal cortices to resolve conflicts and minimize behavioral error by modulating attention, working memory, and motor control processes (Paus, 2001).

**Figure 39.2** Mean arterial pressure (MAP) reactivity to a Stroop color-word interference stressor is shown as a function of gray matter volume and fMRI BOLD activation in the prefrontal cortex, encompassing Brodmann area (BA) 32 of the perigenual anterior cingulate cortex (pACC) and BA 10 of the medial prefrontal cortex. (A) Statistical parametric maps derived from a random-effects analysis illustrating left and right pACC areas where MAP reactivity varied with gray matter volume (determined by voxel-based morphometry). (B) MAP reactivity is shown as a function of mean-centered and sex- and total-grey matter adjusted volume values extracted from the left (L, open circles, dashed line) and right (R, closed circles, solid line) pACC areas shown in A. (C) Statistical parametric maps illustrating left and right pACC areas where greater MAP reactivity varied with greater BOLD activation (D). MAP reactivity is shown as a function of mean-centered and standardized pACC BOLD activation values extracted from the left (open circles, dashed line) and right (closed circles, solid line) pACC areas in (c). *p < 0.01. Reprinted with permission from Gianaros, P. J., Sheu, L. K., Matthews, K. A., Jennings, J. R., Manuck, S. B., & Hariri, A. R. (2008). Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *Journal of Neuroscience, 28*, 990–999. (See color insert.)
evidence further implicates the insula in cortical cardiovascular control via efferent and afferent signaling with networked cortical and subcortical areas important for autonomic regulation (Cechetto, 1994; Oppenheimer, 1993; Verberne & Owens, 1998). Consistent with this evidence, insula activation has been reliably associated with stressor-evoked blood pressure reactivity in several studies (Crichtley et al., 2000; Gianaros et al., 2005, 2007, 2008).

AMYGDALA

The amygdala is composed of distinct cell groups in the medial anterior temporal lobes. As a cell complex, a critical function of the amygdala in stressor-related processing involves the rapid assignment of emotional salience to environmental events (Davis & Whalen, 2001; LeDoux, 2003; Sah, Faber, Lopez De Armentia, & Power, 2003; Zald, 2003). The amygdala supports such processing by integrating multimodal sensory inputs from distributed cortical, thalamic, and brainstem afferent relays. More precisely, sensory input is relayed through thalamic and cortical-thalamic pathways to the basolateral area via the lateral nucleus, basolateral nucleus, and accessory basal nucleus (LeDoux, 2003; Sah et al., 2003). From the basolateral nucleus, motivationally relevant sensory signals are relayed to the central nucleus. As a primary output nucleus, the central nucleus signals commands for adaptive changes in behavior and supporting physiologic adjustments via the stria terminalis to lateral and paraventricular hypothalamic nuclei and to periaqueductal, medullary, and preautonomic nuclei. Importantly, the central nucleus is also networked with cortical areas involved in stressor-related processing, principally, areas of the pACC, dACC, and anterior insula (Amaral & Price, 1984; McDonald, 1998; Morecraft et al., 2007; Price, 2003). Hence, the amygdala is broadly viewed to interrelate cortical processes supporting the coordination of stressor-evoked changes in behavior and peripheral physiologic (e.g., cardiovascular) reactivity (Berntson et al., 1998; Dampney, 1994; Saper, 2002; Smith & DeVito, 1984; Smith, DeVito, & Astley, 1984). In this context, it is noteworthy that a specific pathway by which the amygdala can regulate blood pressure reactivity is via its influence over the baroreflex (Berntson et al., 1998; Dampney, 1994; Saha, 2005).

The baroreflex is a negative feedback control mechanism that constrains mean arterial pressure around a regulatory set point. Specifically, the baroreflex controls beat-by-beat changes in blood pressure by adjusting heart rate, cardiac output, and vascular resistance. As a negative feedback loop, the baroreflex relies on afferent projections from cardiopulmonary mechanoreceptors and chemoreceptors that signal changes (e.g., increases) in blood pressure to the NTS. Afferent activation of the NTS in turn activates vagal nuclei in the medulla and, via signaling with the caudal ventrolateral medulla, inhibits presympathetic nuclei in the rostroventrolateral medulla.

INSULA

The insula is located in the Sylvian fissure and is hidden beneath the frontal, parietal, and temporal opercula. Broadly, the insula—particularly the anterior division—expresses efferent and afferent connections that parallel those of the anterior cingulate, including connections with the amygdala, hypothalamus, thalamus, PAG, pons, nucleus tractus solitarius (NTS), and medullary and brainstem areas that control preautonomic nuclei innervating peripheral target organs (Augustine, 1996; Cechetto, 1994; Ongür & Price, 2000; Verberne & Owens, 1998). Furthermore, afferent relays from all peripheral target organs project to the insula along a caudal-to-rostral extent. These afferent projections are routed via the parabrachial nucleus, ventral posterior and mediodorsal thalamic nuclei, and lateral hypothalamic area, and they provide the insula with a “viscerotopic” map of the body (Craig, 2003, 2005). Such a map has been posited to support the integration of interoceptive information with the appraisal of emotion-related stimuli and contextually adaptive behavioral and autonomic responses (Craig, 2005; Critchley, 2005; Paulus & Stein, 2006). Similar to areas of the cingulate, the insula—particularly the anterior division—is engaged by behavioral challenges that elicit errors (Klein et al., 2007) and by unpleasant emotional stimuli (Feldman-Barrett & Wheeler, 2006; Phan, Wheeler, Taylor, & Liberzon, 2002). Longstanding animal
and intermediolateral column. In effect, these dynamic changes in autonomic control adjust heart rate, cardiac output, and vascular resistance to maintain blood pressure within a homeostatic range (Dampney, 1994).

As shown in the conceptual model of blood pressure reactivity depicted in Figure 39.3, the amygdala can gate the baroreflex via projections that inhibit the NTS and that activate the rostroventrolateral medulla (Berntson et al., 1998; Dampney, 1994; Saha, 2005; Saper, 2002). These projections are routed partly through the hypothalamus, PAG, and dorsal pons. Important in the present context, these amygdala projections are paralleled by similar projections from the anterior cingulate and insula, which can also gate the baroreflex on exposure to acute stressors, allowing blood pressure to exceed its regulatory set point (Berntson et al., 1998; Dampney, 1994; Saper, 2002). Furthermore, it has been hypothesized that the amygdala and networked cortical areas may partly underlie individual differences in cardiovascular reactivity by linking stressor-related processing with mechanisms such as baroreflex suppression (Berntson et al., 1998). Consistent with this idea, there is both recent PET (Critchley et al., 2000) and fMRI (Gianaros, Sheu et al., 2008) evidence that stressor-evoked amygdala activity covaries with blood pressure reactivity (Figure 39.4).

In addition to these functional associations between individual differences in stressor-evoked cardiovascular reactivity and patterns of brain activation, there is recent structural neuroimaging evidence to suggest that cardiovascular reactivity is associated with clinically relevant patterns of brain morphology. For example, Waldstein et al. (2004) reported that exaggerated stressor-evoked increases in blood pressure are associated with markers of subclinical cerebrovascular disease in white matter brain tissue among older individuals, suggesting a potential role for cardiovascular reactivity in disease vulnerability processes measured at the level of gross brain structure.

In aggregate, these functional and structural neuroimaging studies suggest that limbic brain areas, including the cingulate cortex, insula, and amygdala, may be involved in linking stressor-related processing with forms of cardiovascular reactivity, such as stressor-evoked blood pressure reactivity, that may promote CHD risk among vulnerable individuals. An important direction for future work will be to test whether individual differences in the functionality of these brain systems directly predict CHD endpoints or aid in CHD risk stratification or prevention.

**NEUROIMAGING STUDIES OF NEUROENDOCRINE ACTIVITY**

**CORTISOL**

The HPA axis is another major arm of the peripheral stress response system that has been increasingly studied in neuroimaging research, particularly among individuals with stress-related psychiatric disorders such as posttraumatic stress disorder (Liberonz et al., 2007) and among healthy individuals (Eisenberger et al., 2007; Kern et al., 2008; Pruessner et al., 2005, 2007; Urry et al., 2006). As detailed by Lundberg (this volume), several endpoints of the HPA axis can be measured reliably. In particular, cortisol can be measured as it changes from pre- to poststressor periods and as it varies over the course of the day. As illustrated below, individual differences in the functionality of several limbic brain systems discussed above have been linked to both acute (stressor-evoked) and circadian (diurnal) changes in cortisol.

For example, Urry et al. (2006) combined the measurement of diurnal cortisol changes with an experimental paradigm involving emotion regulation. In
In another example of how cortisol can be assessed in association with functional neural activity, Eisenberger et al. (2007) demonstrated that cortisol changes elicited by the Trier Social Stress Task (TSST) administered outside of an MRI scanner were correlated with activation during a social rejection task performed inside of the scanner. Specifically, activation of the dACC and dorsal medial prefrontal cortex was correlated with larger cortisol responses to TSST. Moreover, activity in these limbic areas statistically mediated the association between individual differences in perceived social support and cortisol responses. An intriguing conclusion drawn by the authors was that a person’s level of social support may modulate how specific brain areas regulate stress-related cortisol reactivity (Eisenberger et al., 2007).

Because of the widespread use of the TSST in laboratory studies of cortisol reactivity (Dickerson & Kemeny, 2004), several attempts have been made to emulate key elements of this stressor paradigm in neuroimaging experimental designs. One important adaptation, the Montreal Imaging Stress Task, was developed by Pruessner et al. (Dedovic et al., 2005). In this task, participants solve challenging mental arithmetic problems as in the laboratory version of the TSST, but the problems are presented and solved while participants are inside of a PET or MRI scanner. Social evaluation is provided by negative feedback

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**Figure 39.4** Mean arterial pressure (MAP) reactivity to a Stroop color-word interference stressor is shown as a function of stressor-evoked amygdala activation. (A) Statistical parametric maps illustrating areas of the left and right amygdala where MAP reactivity varied with fMRI BOLD activation. (B) MAP reactivity (change from a resting baseline) is shown as a function of mean-centered and standardized amygdala BOLD activation values extracted from the left (L, open circles, dashed line) and right (R, closed circles, solid line) amygdala areas in (a). *p < 0.01. Reprinted with permission from Gianaros, P. J., Sheu, L. K., Matthews, K. A., Jennings, J. R., Manuck, S. B., & Hariri, A. R. (2008). Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. Journal of Neuroscience, 28, 990–999. (See color insert.)
from a computer program and by the investigator after task performance.

Using the Montreal Imaging Stress Task, Pruessner et al. (2007) reported significant correlations between salivary cortisol changes and relative decreases in brain activity during task performance. These “deactivations” were observed across a number of limbic brain areas, including the hippocampus, amygdala, insula, hypothalamus, and pCC. These findings are notable in that these areas may exert a tonic inhibitory control over the HPA axis. Thus, when “deactivated” under stress, such areas may disinhibit the release of cortisol by the HPA axis.

Using a similar mental arithmetic stress task with negative feedback administered during perfusion MRI, Wang et al. (2005) found that activation in the right ventral prefrontal cortex (RVPFC), insula, and putamen—brain areas linked to emotion regulation processes—was associated with task-related subjective stress ratings. Furthermore, sustained activity in RVPFC and dACC after the task covaried with participants’ cortisol responses assessed during imaging. However, later analyses of the same data (Wang et al., 2007) suggested that these correlations may have been sex specific. In women, the stress task seemed primarily to elicit activation of the ventral striatum, putamen, and insula, with dACC and pCC activation persisting beyond the task relative to men. Furthermore, in women, significant associations were observed between cortisol reactivity and dACC activity. In men, the stress task primarily elicited activation of the RVPFC and suppression of left orbital frontal cortex, which also persisted beyond the task relative to women. The authors tentatively linked their findings with a sex-specific stress model for “fight or flight” in men and “tend and befriend” in women (see Taylor, this volume). Broadly stated, these findings highlighted the importance of assessing sex differences in centrally mediated stress reactivity because men and women may differ in the expression of cognitive, behavioral, social, and physiologic stress processes underlying observed patterns of reactivity.

**OXYTOCIN**

In addition to cortisol, several recent neuroimaging studies of neuroendocrine functioning have examined functional neural activity in association with oxytocin. Oxytocin is a neuropeptide important for social bonding and attachment. Oxytocin is implicated in the suppression of anxiety to psychosocial stress and in the enhancement of trust (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Oxytocin is being studied increasingly in neuroimaging research because of its potential role in centrally mediating social support mechanisms buffering against psychological stress. Because oxytocin can be administered intranasally and because it crosses the blood–brain barrier, the influence of oxytocin on functional brain activity can be measured in neuroimaging paradigms. For example, Kirsch et al. (2005) reported that amygdala activity is reduced in response to fear-inducing visual stimuli in healthy males after intranasal administration of oxytocin. However, Domes et al. (2007) later reported that amygdala activity is reduced by oxytocin in response to angry, fearful, and happy faces, suggesting that oxytocin may affect the processing of emotionally salient social stimuli in general and not just “threat”- or “stress”-specific stimuli in particular. Domes et al. speculated that such a mechanism mediated by oxytocin may facilitate social approach behavior in the context of both positive and negative emotional circumstances. More broadly, these findings highlight the importance of considering both positive and negative emotional stimuli in studies of stress research.

**STUDIES OF CHRONIC STRESS PROCESSES**

**FUNCTIONAL NEUROIMAGING RESEARCH ON BEREAVEMENT**

Bereavement, or the period after the death of a close person, provides an opportunity to study a common, ongoing stressful life event that can become chronic. Grief experienced during bereavement comprises the emotional, physiologic, and behavioral response to the death of a close person, which can be intense for many. However, most will adapt to their loss, with the intensity of grief waning with time (Bonnano et al., 2002). Stress- and grief-related factors occurring during bereavement have long been associated with negative physical health outcomes (Kraus & Lilienfeld, 1959), with several studies showing moderate, but reliable, associations between bereavement and morbidity and mortality rates (Stroebe, Schut, & Stroebe, 2007). Bereavement and grief are experienced by nearly everyone and thus can be studied in among those who are mentally and physically healthy.

Evoking grief in bereaved individuals during neuroimaging is one way to evaluate the potential neurobiological pathways linking bereavement and health. This has been done using personalized stimuli to evoke grief in blocked neuroimaging paradigms (Gündel et al., 2003). Stimuli that are personally relevant (such as pictures of a deceased family member) are likely to elicit strong negative emotions comprising the experience of grief. To facilitate the study of grief, O’Connor and colleagues created grief stimuli using photos of the deceased provided by study participants (Gündel et al., 2003; O’Connor et al., in press). These photos were then matched with photos of a stranger to serve as stimuli for a neutral comparison condition in a blocked fMRI design. In addition, grief-related words from participants’ narratives were matched with neutral words on several potentially confounding factors, including number of letters, number of syllables, parts of speech, and usage frequency in the language. These words
and pictures were then shown simultaneously to participants during testing. By creating composites of pictures and words, a 2 × 2 design can be used in studies examining the differential activity between four conditions (1, deceased-grief word; 2, stranger-grief word; 3, deceased-neutral word; 4, stranger-neutral word) (Figure 39.5).

In one study using this grief-eliciting paradigm, responses to the grief versus neutral stimuli were first assessed both by self-report and by changes in skin conductance, which reflects sympathetic nervous system outflow to the eccrine sweat glands (Gündel et al., 2003). Graded responses across the four conditions were detected for both self-reports and skin conductance, such that neutral words paired with photos of strangers produced the weakest responses, and grief words paired with photos of the deceased produced the strongest responses.

Figure 39.5: Results from a functional neuroimaging study of grief in bereaved individuals: (A) Subjective grief ratings of eight bereaved women viewing words and pictures related or unrelated to a deceased relative. Grief-related stimuli elicited stronger subjective responses than the non-grief-related stimuli. (B) Skin conductance (electrodermal) responses of the women viewing the same composites of words and pictures. As for subjective ratings, grief-related stimuli elicited stronger electrodermal responses than the non-grief-related stimuli. (C) Brain images showing activated areas in the women when they viewed grief-related words (Word Factor) in the picture-word composites. Areas demarcated by cross-hairs are the posterior cingulate cortex (retrosplenial cortex) and medial prefrontal cortex. (D) Brain images showing areas activated in response to a photograph of their deceased relative (Person Factor) in picture-word composites. Brain area demarcated by the cross-hairs is the dorsal anterior cingulate cortex. Reprinted with permission from Gündel, H., O’Connor, M.-F., Littrell, L., Fort, C., & Lane, R. D. (2003). Functional neuroanatomy of grief: An fMRI study. American Journal of Psychiatry, 160, 1946–1953. (See color insert.)
across measures. These observations provided the basis for subsequent neuroimaging results to be interpreted as correlates of these bereavement-related subjective and physiologic changes.

Hence, in an fMRI subtraction paradigm used within an event-related experimental design, patterns of brain activation that were associated with the picture and word factor contrast localized brain activation in several limbic brain regions discussed above, including the dACC, pCC, and insula. Together, these findings suggested that acute experiences of grief may be characterized by activity changes in a distributed network supporting emotional information processing, episodic memory retrieval, processing familiar faces, visual imagery, and the modulation/coordination of these functions.

In a recent extension of this work (O’Connor et al., 2008), bereaved individuals with complicated (prolonged and unresolved) grief were compared with those with noncomplicated grief in an event-related fMRI paradigm. As predicted based on previous work, both groups showed BOLD activation in areas sensitive to social pain (e.g., the dACC) in response to reminders (pictures and words) of their relatives who had died of breast cancer. Notably, women experiencing complicated grief showed increased activation of the nucleus accumbens, a central component of a distributed reward-related striatal circuit. Moreover, greater nucleus accumbens activity covaried with greater levels of self-reported yearning, and not time since death, age, and positive/negative affect. These results were interpreted within a conceptual framework, suggesting that persistent attachment during bereavement is associated with greater activity in reward systems, such as the nucleus accumbens, which could reflect dysregulated adaptation to losing a loved one. Together, these studies of bereavement offer examples of the application of neuroimaging methods to understand chronic or ongoing stress processes in a population at risk for adverse health outcomes.

STRUCTURAL NEUROIMAGING STUDIES OF CHRONIC LIFE STRESS

Complementing functional neuroimaging studies of the stress-related processes reviewed above, a growing number of structural neuroimaging studies have begun to examine longer-term or chronic stress-related and psychosocial factors in association with aspects of brain morphology, particularly brain tissue volume. Much of this work is based on an extensive animal literature documenting the effects of chronic and early life stress on markers of brain and neural morphology. In particular, a number of animal models demonstrate that chronic stressful experiences (e.g., prolonged immobilization, housing in dominance hierarchies, and early maternal separation) can remodel neurons and result in changes in the gross morphology of several limbic areas, most reliably areas of the prefrontal cortex and hippocampus. For example, prolonged immobilization simplifies the branching complexity and shortens the length of dendrites of pyramidal neurons in the rat prefrontal cortex (McEwen, 2007). In both rodent and non-human primate models, chronic stressors also remodel neurons in the hippocampus and arrest the proliferation of new neurons, two types of cellular changes that may partly contribute to a decrease in hippocampal volume (Fuchs & Flugge, 2003; McEwen, 2007). Such stress-related changes in the morphology of areas in the cortex and hippocampus can result from alterations in central glucocorticoid levels and receptor densities, acting in conjunction with alterations in the transmission and expression of excitatory amino acids and neurotrophic factors that regulate cellular plasticity and neurogenesis (Fuchs & Flugge, 2003; McEwen, 2000a, 2000b; Sapolsky, 2005b).

In parallel to animal evidence, there is indirect human structural neuroimaging evidence that stressful experiences may be associated with morphologic changes in several brain areas. For example, individuals with stress-related psychiatric disorders, such as major depressive disorder and posttraumatic stress disorder, consistently show volumetric changes of the prefrontal cortex and other limbic brain areas, including the hippocampus (Fuchs & Flugge, 2003; McEwen, 2007). In addition to patient studies, there is emerging evidence for a relationship between stressful experiences and limbic morphologic changes. For example, among otherwise healthy postmenopausal women, higher levels of chronic perceived stress, as measured over an approximate 20-year period of life, have been associated with reduced gray matter volume in the hippocampus and orbitofrontal prefrontal cortex (Gianaros et al., 2007). Furthermore, more than three years after the terrorist attacks on the World Trade Center buildings on September 11, 2001, otherwise healthy adults living in close proximity to the buildings showed reduced gray matter volume in the amygdala, hippocampus, insula, anterior cingulate, and medial prefrontal cortex (Ganzel, Kim, Glover, & Temple, 2008). Finally, there is evidence from healthy adults that the perception of holding a lower social standing than others, a putative source of life stress, is associated with reduced gray matter volume in the anterior cingulate cortex (Gianaros, Horenstein, et al., 2007).

Without longitudinal evidence, however, it has not yet been established that stress-related variation in brain morphology in patient or healthy adult populations is invariably the consequence of so-called “neurotoxic” chronic stress-related mechanisms (Sapolsky, 1996, 2002). It is possible, for example, that preexisting individual differences in limbic brain morphology partly increase vulnerability and sensitivity to life stress and traumatic events (Lupien et al., 2007). These individual differences might emerge early in life and result from a combination of genetic and developmental influences. In line with this notion, there is recent evidence that individual differences in self-esteem and locus of control, which emerge early in life and modify the appraisal of environmental demands,
are associated with hippocampal volume and cortisol changes in both young and elderly people (Pruessner et al., 2005). Furthermore, there is evidence that birth weight predicts hippocampal volume in adulthood, particularly among women reporting low maternal care, suggesting that the postnatal environment may affect neurodevelopmental consequences of prenatal risk (Buss et al., 2007). Finally, otherwise healthy adults reporting that they were exposed to more frequent early traumatic and adverse childhood events show smaller volumes of the anterior cingulate cortex and caudate volumes than those not reporting exposure to such events, further suggesting the important influence of early developmental processes affecting brain morphology and possibly later vulnerability to life stress (Cohen et al., 2006). In aggregate, these structural neuroimaging studies complement functional neuroimaging studies of stress processes in that they may reveal both vulnerability and experience-dependent patterns of brain morphology relevant to risk for and resilience against ill health.

CONCLUSION

We close with a quote from Herbert Weiner, a leading researcher on stress and health whose death came just before the widespread availability of functional neuroimaging. In Perturbing the Organism: Biology of the Stressful Experience, Weiner wrote “The neuronal links between stressful environments and changes in behavior and bodily function are being forged: The ‘black box’—the brain—is not as impenetrable as it once was! (Weiner, 1992, p. xii).” We hope that we have illustrated that this enthusiastic statement is even truer today than it was in 1992. With neuroimaging methods, stress researchers are poised to define the “neuronal links” between stressful experiences and neurobiological processes impacting health and well-being throughout life. In this chapter, we attempted to provide an overview of how functional and structural neuroimaging methods can be specifically incorporated into human stress science. With continued development and integration with other multilevel social, cognitive, behavioral, and physiologic assessment methods, neuroimaging methods will offer opportunities to better explicate the neurobehavioral pathways linking stress-related processes instantiated in the brain to health. In this regard, there are a number of open questions for future research that can be addressed by incorporating neuroimaging methods in human stress science. For example, we know little about how stressor appraisal and coping processes are instantiated in the developing and aging human brain; how stress appraisal, coping, and response processes interact with genetic and environmental factors to influence aspects of brain functionality and morphology influencing mental and physical disease risk; how stress appraisal, coping, and response processes interact with specific forms of emotional experience and emotion regulation; and how markers of brain functionality and morphology may contribute to our understanding of disease etiology and risk stratification. To address these questions, it will be important for stress scientists interested in neuroimaging methods to collaborate as members of multidisciplinary teams operating within multilevel frameworks.

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Annual Meeting of the American Psychosomatic Society, Baltimore, MD.


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