The Rebirth of Neuroscience in Psychosomatic Medicine, Part I: Historical Context, Methods, and Relevant Basic Science

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Neuroscience was an integral part of psychosomatic medicine at its inception in the early 20th century. Since the mid-20th century, however, psychosomatic research has largely ignored the brain. The field of neuroscience has burgeoned in recent years largely because a variety of powerful new methods have become available. Many of these methods allow for the noninvasive study of the living human brain and thus are potentially available for integration into psychosomatic medicine research at this time. In this first paper we examine various methods available for human neuroscientific investigation and discuss their relative strengths and weaknesses. We next review some basic functional neuroanatomy involving structures that are increasingly being identified as relevant for psychosomatic processes. We then discuss, and provide examples of, how the brain influences end organs through “information transfer systems,” including the autonomic, neuroendocrine, and immune systems. The evidence currently available suggests that neuroscience holds great promise for advancing the goal of understanding the mechanisms by which psychosocial variables influence physical disease outcomes. An increased focus on such mechanistic research in psychosomatic medicine is needed to further its acceptance into the field of medicine. Key words: neuroscience, brain imaging, information transfer systems, autonomic nervous system, neuroendocrinology, psychoneuroimmunology.

ACC = anterior cingulate cortex; ALS = anterolateral system; ANS = autonomic nervous system; BOLD = blood oxygen level dependent; CANTAB = Cambridge Neuropsychological Test Automated Battery; CBF = cerebral blood flow; CNS = central nervous system; CRH = corticotropin-releasing hormone; CT = computed tomography; ECG = electrocardiography; EEG = electroencephalography; ERPs = event-related potentials; fMRI = functional magnetic resonance imaging; HIV = human immunodeficiency virus; HPA = hypothalamic pituitary axis; MEG = magnetoencephalography; MRI = magnetic resonance imaging; NKC = natural killer cells; SPECT = single photon emission computed tomography.

“The question which now arises is whether an ominous and persistent state of fear can end the life of a man.”

From “Voodoo Death,” Walter Cannon, 1942 (1)

INTRODUCTION

What are the biological mechanisms whereby emotions, cognitions, behaviors, or social factors are translated into a physical disease process or even death? How can physical disease result in altered emotion, cognition, or behavior? We contend that these questions cannot be answered without studying the brain. Given the prevalence of these types of questions in psychosomatic medicine, such as the one posed by Cannon (1) so long ago, it is surprising that there is so little focus on the mechanistic role of the brain. This is in striking contrast to the earliest theorizing in the field that focused on the critical role of the brain in psychosomatic medicine.

Early in the 20th century, Cannon suggested that the physiology of emotion provided a key link between mental states and physical disease (2). He pointed out that subcortically generated emotion could be routed downstream to the hypothalamus to influence peripheral physiological expression, or travel upstream to the neocortex for symbolic representation and expression. In 1937, Papez (3) presented the first neurological model of emotion that described a reverberating circuit of cortical and subcortical structures that processed information from the environment and the body proper. In 1949, MacLean (4) extended Papez’s model and a few years later (1952) coined the term “limbic system” (5). In his seminal paper in this journal in 1949, MacLean (4) hypothesized that psychosomatic disorders resulted from impaired communication between the limbic system and neocortex. Unfortunately, the ability to test MacLean’s and other brain-based hypotheses was limited at the time by the fact that methods had not yet been developed to noninvasively study the function of the living human brain. Perhaps this is the reason why research in psychosomatic medicine in recent years has tended to ignore the brain. A major reason for reintroducing the brain into psychosomatic medicine at this time is because methods for studying brain structure and function are now readily available and are generating a multitude of important new findings.

Another key reason for a renewed focus on the brain involves the pressing need to enhance the mechanistic focus of our scientific work. At about the same time in the mid-20th century as MacLean’s landmark paper, Alexander (6) in Chicago formulated the theory that specific psychological conflicts contributed to the development of specific medical
disorders. Although appealing because it attempted to address
the influence of the mind on disease in a manner comparable
to the “germ theory” of infectious disease (7), this “Specificity
Theory” proved incapable of handling the many factors that
contributed to disease progression in a particular individual
(8). A more comprehensive “biopsychosocial” model was
introduced that was better able to account for the many factors
that contributed to disease progression (9). As part of this
model, Engel offered the premise that there are critical inter-
relations among biological, psychological, and social systems
that influence health and disease processes. Present day psy-
chosomatic medicine is predicated largely on the study of such
interrelations. Yet, the biopsychosocial model lacks specific-
ity, and the resulting correlational research so common in our
field often falls short of the demonstration of possible causal
mechanisms (10). Psychosomatic medical research is some-
times viewed as not having sufficient mechanistic credibility
in our research so common in our field often falls short of the
demonstration of possible causal mechanisms (11). We propose
that reintroducing the brain into psychosomatic medicine will
enable us to come closer to identifying specific causal mech-
nisms that connect cognitive and emotional functioning—the
mind— to the regulation of peripheral biological phenomena
and will further enhance an etiologic focus in our work.

A complete mechanistic account of psychosomatic disor-
ders will span genes to society, and both human and animal
research will be necessary. Above all, this research must be
integrative in the sense that the biological mechanisms that
link psychological and social factors to the body must be
specified. We hold that this must necessarily include the brain,
and until it does, a complete mechanistic account will not be
possible. If we turn to the fields of cognitive, affective, and
social neuroscience, we begin to derive answers to questions
regarding the relationships of brain structure and function to
mental states. Research in psychosomatic medicine has fre-
quently linked mental states to peripheral physiological
processes. However, few investigations have incorporated
measures of cognitive, affective, or behavioral processes,
brain, and peripheral physiology. It is the interrelations
among these measures that will be critical in establishing
possible mechanistic linkages to disease end points. By further
incorporating the body of knowledge and methodologies em-
anating from relevant fields of neuroscience into our research
in psychosomatic medicine, we can move this field closer to
identifying the specific mechanisms that link mental function-
ing to health and disease.

This paper aims to provide an overview of neuroscience for
psychosomatic researchers and clinicians who are not neuro-
scientists. We will first assess the state of the art in neuro-
science methods as it relates to psychosomatic medicine.
Next, in discussing pathways from mind to body, we will use
the following classification system for different levels of func-
tion: A) mental/psychological/behavioral states and traits; B)
brain; C) information transfer systems (autonomic nervous
system [ANS], endocrine, immune); and D) body proper (end
organ function and dysfunction). Psychosomatic medicine
currently focuses on levels A, C, and D. It is our thesis that the
mind (A) can influence the body (D) only through levels B
and C. We will therefore focus on level B and its relationship
to level A, and will examine what is known about the relation-
ship of B to C. In a companion paper (12), we illustrate the
applicability of this approach in the context of cardiovascular
disease, functional gastrointestinal disorders, pain, and pla-
cebo, and we conclude by discussing the implications of this
approach for research and practice. We focus here on “molar
neuroscience” (brain imaging, neuroanatomy, etc.), but we
expect that, as the field evolves, a molecular level of analysis
(genes, proteins, receptors, etc.) will be integrated and will
extend our understanding even further.

Neuroscience Methods Relevant to
Psychosomatic Medicine

The psychosomatic approach has always sought to infer
linkages between psychological and neurophysiological pro-
cesses influencing health and disease. Yet, these inferences
have been limited by the validity and resolution of the meth-
ods available. The largest share of current psychosomatic
research infers mediation by the brain (level B) from relation-
ships between behavioral traits (level A) and disease state
(level D). Consider, for example, the presumption that brain
processes mediate the relationship between depression and
morbidity or mortality (13). The processes underlying this
association remain unidentified. Adding an information tran-
fer measure (level C) adds to our understanding. For example,
acute stress effects on the immune system, presumably medi-
ated by the brain, may differ between depressed and nonde-
pressed individuals (14). Our knowledge of brain control of
the immune system and the brain processes involved in de-
pression can help to develop our hypotheses in studying this
phenomenon (15). Yet, the critical changes in brain processes
that yield an effect on immune processes during depression
remain largely undefined without level B measurements. Stud-
ies that link mental states to brain function and peripheral
physiological systems are essential, and they can be enriched
by neuroscience techniques that identify the intervening pro-
cesses between psychological manipulation and behavioral or
information transfer system change.

Substantial advances in brain imaging have occurred in the
past two to three decades. Use of currently available methods
promises to yield an immeasurable increase in our knowledge
of how the brain acts to foster health and hinder disease. We
will confine this discussion to the investigation of the human
brain. Here, we examine methods that have potential applica-
tions to, but are underutilized in, psychosomatic research.

Assessment of Brain Structure

Lesion Studies

Study of persons with a naturally occurring brain lesion due
to stroke or tumor allows examination of pertinent associa-
tions with behavior, bodily regulation, and brain function (16).
For example, select studies have found that right hemisphere
lesions diminish autonomic responses to emotional stimuli
(17,18). Interpretation of such clinical material is aided if
findings can be compared with studies in experimental animals and if the spatial location of the lesion can be specified, using structural imaging techniques. A major drawback is that naturally occurring brain lesions are not typically confined to distinct neuroanatomical boundaries; additional lesions may be present; connecting fibers rather than regions may be the source of altered function; and postinsult neuroplasticity may alter the function of a region.

Computed tomography (CT) imaging consists of noninvasively creating a three-dimensional picture of brain structure, using x-ray radiation (19). The CT camera delivers x-rays to the brain from multiple angles and records variations in x-ray penetration to the opposite side of the head. One picture from each angle is comparable to a chest radiograph in terms of capturing variations in density of the tissue being imaged, but by using a computer to combine views from multiple angles, a three-dimensional picture of the brain is generated. CT imaging is particularly good for identification of select pathologic processes, such as bleeding within the brain. However, it is limited in its ability to characterize brain morphology and subtle pathology.

Magnetic Resonance Imaging (MRI)

MRI techniques (20), which include structural, functional, chemical, and tract tracing methods, involve varying the timing, pattern, and vectors of magnetic fields to interact with specific chemicals in the brain, such as hydrogen ions. After the head is placed in a powerful magnetic field, radiofrequency signals (i.e., electromagnetic radiation that has low energy, long wavelengths, and is nonionizing) are delivered to the brain. Resultant radio waves are then emitted, recorded, and used to create the images. The specific combination of magnetic field manipulations and radiofrequency inputs, called a “pulse sequence,” can be manipulated to favor the type of process one seeks to visualize. Structural MRI can readily show the investigator the gross anatomy of gray and white matter in the brain and associated brain pathology, and can manipulate the images to display anatomical slices or other depictions of use. These images can then be visually rated, measured by an observer, or computer scored to provide high-quality information on brain anatomy and subtle brain pathology, such as white matter disease and silent brain infarction. Diffusion tensor imaging is a specialized MRI technique that capitalizes on the diffusion of water molecules along fiber tracts and provides detailed information on the integrity and connectivity of white matter tracts.

Obtaining information on brain anatomy and pathology is particularly relevant to the influence of chronic diseases on the brain. For example, individuals with various cardiovascular risk factors and diseases, and increased stress-induced cardiovascular responses, frequently display silent cerebrovascular disease on MRI in the absence of clinical stroke (21–23). Prolonged stressors may influence brain anatomy (24), as in the relation of persistently high levels of cortisol to decreased hippocampal volume (25). An aggregation of white matter disease may disrupt information processing relevant to daily life (26), has been associated with late-life onset depression (i.e., the vascular depression hypothesis) (27), and is associated with indices of ANS dysregulation (28).

Structural MRI offers slightly better spatial resolution than CT, but much better contrast resolution. Thus, it is better at characterizing anatomy and most pathology. Another significant advantage is that, unlike CT, it does not involve ionizing radiation. Relative disadvantages of structural MRI are that it costs more than CT and cannot be used in patients who have metal devices or objects in their bodies. Metal distorts the magnetic fields generated by the MRI scanner that are essential for creating its images, and radiofrequency pulses can heat metal that can damage adjacent tissue.

Assessment of Brain Function

Various methods for measuring brain function are displayed in Figure 1. Each method is depicted relative to the others on logarithmic scales of spatial resolution (how small or large is the brain area captured by the technique) and temporal resolution (how small or large is the unit of time over which brain activity is captured). It is notable that each technique is associated with a range of spatial and temporal resolutions, and each technique has its own unique profile or footprint on this grid. Thus, each method has its own unique advantages and disadvantages. Although each technique is used on its own, combining techniques enables an investigator to capitalize on the advantages of each to study a given process. For example, functional MRI (fMRI) provides excellent spatial localization of brain function but less precise temporal information, whereas electroencephalography (EEG) and event-related potentials (ERPs) enable more precise measurements of a process in time but have poorer spatial resolution than fMRI. Therefore, using the combination of both methods permits the investigator to capitalize on the advantages of each.

EEG/ERPs

The EEG, or measurement of brain electrical activity from electrodes placed on the scalp, provides an excellent index of degree of brain activation, particularly in cortical (as opposed to subcortical) regions. Variations in sleep and affective states are known to yield substantial differences in the frequency and patterns of the electrical activity. For example, asymmetric right prefrontal activation during negative emotional states and asymmetric left prefrontal activation during positive emotional states have been observed (29,30) and emotion-induced brain activation assessed by EEG has been linked to patterns of ANS arousal (31).

Further information can be garnered by examining the response of the brain to stimulating events. The synchrony of response across regions of the brain can be examined in conjunction with the averaged response to the event. This method, known as the ERP, can be assessed across electrodes encompassing most of the scalp (32). Components of the event-related response can provide information on processes such as attention, perceptual discrimination, and sensitivity to
Motivational/affective manipulations modulate such processes and can be detected in the ERP. Recent work has demonstrated enhanced ERP activity when individuals read personally tailored intervention material as compared with nontailored material (33).

A major strength of EEG and ERP is their excellent temporal resolution. These techniques offer close temporal proximity of the eliciting stimulus, psychological processing, and the observed electrocortical response, by offering the ability to record in real time with millisecond accuracy. However, EEG offers limited anatomic specificity, given the complexity of the generation of the electrical change and its transmission within the brain. The anatomical source of an electrical change at the scalp can only be inferred with difficulty and some remaining uncertainty (34). The inference of signal source is, however, improving and progress is being made in understanding connectivity patterns from the mass of joint time series obtained from as many as 128 electrodes placed on the scalp.

Magnetoencephalography (MEG), a less widely available and more expensive technique, senses magnetic field changes within the brain using very sensitive, super-cooled magnets (35). This method exploits the fact that magnetic fields pass through the skull and meninges unimpeded, unlike the electrical signals that make up the EEG, which encounter high levels of resistance and thus signal attenuation by the structures that protect the brain. The temporal resolution of the obtained signal is equal to that of the EEG, enabling the continuous recording of brain activity in real time, and spatial localization of the source of observed changes is superior to that of the EEG. However, the strength of magnetic fields declines exponentially with distance. Hence, MEG is an excellent tool for examining local activity at the level of the cortex but limited in its ability to detect activity deeper in the brain. Recent applications have shown that the anticipation of affective stimuli can readily be detected with this technique in both healthy individuals and patients with schizophrenia (36,37).

**Positron Emission Tomography (PET) and fMRI**

Perhaps the most significant methodological development for psychosomatic medicine has been the ability to visualize regional brain activation using PET and fMRI (see references 19,20 for primers on these techniques). Both techniques provide better spatial resolution than EEG but poorer temporal resolution. As depicted in Figure 1, fMRI has slightly better spatial resolution at roughly 3 mm than PET at 3 to 10 mm. PET became available for functional brain imaging over a decade before fMRI but fMRI is now the most commonly used technique for studying regional brain activity. PET in combination with short half-life radiotracers, such as $^{15}$O-water and fMRI, both exploit the fact that when neuronal activity in a brain area becomes more active, blood flow to that brain area increases, peaks at about 8 seconds, and returns to baseline about 8 seconds later if stimulation is not sus-
tained. These two techniques have revolutionized our understanding of how mental functions are instantiated in the brain because the scale of measurement, the entire brain, permits the detection of activity in the spatially distributed neural networks that actually execute the cognitive and emotional mental states under investigation (38). As such, we now have a much greater ability to understand the role of level B in psychosomatic phenomena.

PET requires the administration of a radioactive tracer whose uptake in tissue can be identified and localized based on high-energy photon emission. PET radiotracers are unstable isotopes that decay at specific rates (half-lives). When these radiotracers decay, they emit positrons (equivalent to an electron except positively charged) that collide with electrons. When the collision occurs, the particles annihilate each other and mass is converted to energy (photons), according to Einstein’s classic $E = mc^2$ equation. Similar to CT, a computer generates a three-dimensional picture from these emitted photons. The photons emitted by PET are gamma rays, which are shorter wavelength and higher energy than x-rays. The amount of radiation exposure to the subject in a research study is not considered dangerous (e.g., well below levels thought to increase risk of cancer). Tracers vary in their specificity and half-lives (19). For example, the tracer $^{15}$O-water has a half-life of 2 minutes, follows oxygen delivery to the tissue (due to blood flow), and is well suited for imaging the brain as many as 10 to 12 times in a session, e.g., multiple inductions of emotional and control states spaced roughly 10 minutes apart. $^{18}$Fluorine-labeled deoxy-glucose as a tracer has a half-life of 110 minutes, follows the metabolism of glucose in brain tissue, and is well suited for imaging metabolic function in neurons over substantial periods, e.g., during a sleep stage. Using variants of the Fick principle and arterial blood measurement, PET can provide quantitative estimates of cerebral blood flow (CBF) on an absolute scale. In the absence of a simultaneous measure of radioactivity in the blood, PET provides information about relative activity in one brain region compared with another.

PET radiotracers can be incorporated into any organic molecule. Hence, the potential to use PET to track molecular processes in the brain is virtually unlimited. The development of ligands (radioactive tracers) with affinities for specific brain constituents provides the opportunity for in vivo studies of, for example, receptors, neurotransmitters, medication effects, or pathological processes. Such development (focused on ligand magnetic properties) is also ongoing in MRI research. MRI results have, however, been more difficult to quantify in terms of specific physiological parameters than PET. Thus, PET is more versatile than fMRI in that it can be used to study blood flow, glucose metabolism, receptor density, neurotransmitter mechanisms, and other processes.

fMRI examines the degree of regional blood oxygenation (commonly referred to as BOLD for “blood oxygen level dependent” activity) which varies with the activation of neural tissue. The BOLD signal is closely related to, although not exactly equivalent to, blood flow to a particular brain region. fMRI exploits the fact that the hemoglobin molecule, which contains iron and carries oxygen to the tissue, varies in its strength as a magnet as a function of whether it is oxygenated (more plentiful when blood flow increases to an area) or deoxygenated (more plentiful when brain tissue is less activated). Images based on the difference in signal between an experimental (activated) and control (not activated) condition show the activation present during the type of information processing under investigation, e.g., sensory, affective, mnemonic, or motor.

An important aspect of neuroimaging research in psychosomatic medicine is to simultaneously record ongoing peripheral physiological processes. A distinct advantage of PET for psychosomatic researchers is that one can record peripheral physiology without the imaging technique interfering with the recording, or vice versa, whereas such interference is a major issue with fMRI. The biggest obstacle in the fMRI context is that the changing magnetic gradients inherent in fMRI imaging induce dense electrical artifact on physiological recordings such as the electrocardiogram (ECG) that is not removed by simple filtering of the signal. A second major obstacle is that none of the equipment used to obtain and record the peripheral signal can contain metal. However, major efforts have been made to develop methods for psychophysiological recordings during fMRI. In that regard, techniques are currently available to simultaneously record EEG, ECG, blood pressure, respiration, and skin conductance during fMRI. Some of these techniques require special equipment that is expensive and some (e.g., continuous blood pressure measurement) are very new and not yet widely available. Nevertheless, the long-term future for research in this area is very promising. For example, recent findings indicate that fMRI activation of select cortical and subcortical regions (e.g., perigenual and posterior cingulate cortex, prefrontal cortex) is associated with greater stress-induced blood pressure responses (39). Further, increases in regional CBF in the subgenual anterior cingulate cortex (ACC) (Figure 2), assessed by PET, during working memory tasks have been related to increases in the vagal (high-frequency) component of heart rate variability (40).

fMRI has several advantages over PET including better spatial and temporal resolution, no ionizing radiation, and roughly one-fourth the cost per subject. Thus, if the BOLD signal captures the phenomenon of interest, it is preferable to PET measures of CBF. Both techniques are highly subject to motion artifact, and claustrophobia can interfere with participants’ ability to endure the associated apparatus (particularly in fMRI). fMRI is also subject to distortion of signal in ventral prefrontal and medial temporal regions (called “magnetic susceptibility artifact”), although technical advances have largely overcome this limitation.

The observation of active areas with imaging provides static information that does not directly reveal how these areas are organized to activate or inhibit each other or show the temporal dynamics of activation. This is especially relevant in light of evidence that both normal (e.g., learning) and abnormal (e.g., peripheral nerve damage) functioning can lead to
demonstrable brain reorganization (41). Techniques such as structural equation modeling are increasingly being used to demonstrate the magnitude and the direction of influence of the components of the neural circuits that execute complex cognitive and emotional functions (42). Combining such techniques with advances in the temporal and spatial resolution of
imaging promises to advance understanding of how different brain areas actually work together to instantiate mental events.

Other Measures of Brain Function

Several other methods have been used to assess (largely) resting measures of cerebral perfusion. These include single photon emission CT (SPECT), xenon inhalation CT, and new MRI methods including perfusion-weighted imaging, diffusion-weighted imaging, and arterial spin labeling. Magnetic resonance spectroscopy involves adjustment of the MR pulse sequence to assess the concentration of chemical substances. This technique has reasonable anatomical specificity and can be used to estimate neurotransmitter concentrations and neuronal viability.

Transcranial magnetic stimulation (TMS) is not a functional imaging technique per se but is a technique for probing regional functional activity. TMS involves the focal delivery of magnetic fields from the surface of the head to specific areas of the cortex. The magnetic fields induce electrical currents in neurons that can either stimulate or inhibit the cortical tissue. The area stimulated is about equal to the size of the thumb. TMS can be used to induce fully reversible inactivation of cortical areas for several minutes for experimental study as well as treatment for conditions, such as depression (43).

Optical imaging is a less expensive technique that refers to infrared and near spectrum examination of the brain, using light reflectance or transmission. One technique is based on neural change per se and therefore has good temporal and spatial resolution (but limited depth) (44). The other technique, near infrared spectroscopy, is directed largely at CBF and has reduced temporal resolution for this reason.

Depth electrodes can be placed directly into the brain tissue of patients for monitoring, stimulation, or both. For example, recording neuronal activity in multiple locations has been used to examine the brain structures that participate in temporal lobe seizures associated with the experience of fear or its absence (45). The direct electrical stimulation of the subthalamic nucleus is a well-established technique for symptomatic improvement of patients with medically intractable Parkinson’s disease. This basic approach was successfully adapted for the treatment of refractory depression by implanting electrodes into and stimulating the subgenual ACC (46).

Neuropsychological Tests

Modern neuropsychological testing focuses on characterizing patterns of performance in multiple domains of cognitive function. Results of neuroimaging studies confirm that performance of specific tests may reflect select underlying brain structures and processes or “systems.” Thus, neuropsychological tests offer an indirect way to examine brain function, and can complement structural and functional neuroimaging procedures. Recently developed tests are often targeted to particular processes, such as frontal lobe dysfunction. For example, one battery, the CANTAB (Cambridge Neuropsychological Test Automated Battery), seems to assess frontal lobe functions reasonably well, although it may not be as powerful at separating individual differences in brain neurochemical systems, as initially thought (47). Alterations in neuropsychological test performance, ranging from mild to severe, have been associated with a multitude of medical and psychiatric conditions (31,48).

Brain Basis of Mental States Relevant to Psychosomatic Medicine

The advent of the neuroscience methods described above has ushered in a new era in which the brain basis of mental states relevant to psychosomatic medicine can begin to be identified. Space does not permit a comprehensive discussion of the many psychological, behavioral, and social factors relevant to our field, each of which may have its own instantiation in the brain. Nevertheless, it may be useful to review some of the highlights of the discoveries in this area to give readers unfamiliar with neuroscience a sense of how rapidly the field is progressing, and the potential that lies ahead (49–52).

Functional Neuroanatomic Bases of Mental States

Brain organization can be thought of in a hierarchical manner. The lower portions of the brain, including the brainstem, midbrain, and hypothalamus, control vital bodily processes necessary for the sustenance of life. People with severe brain damage who are not in conscious contact with the outside world nevertheless can continue to live indefinitely in what is called a “chronic vegetative state” due to ongoing activity in these primitive structures at the base of the brain. These are also the regions where autonomic, endocrine, and perhaps immune responses are regulated (we know much less about the neural regulation of immune function than about autonomic and endocrine regulation); thus, they are thought to serve a critical role in linking activity in higher brain centers to peripheral physiological systems in health as well as disease. The advent of functional imaging and related techniques has made it possible to observe activity in brainstem nuclei and the hypothalamus (53). The spatial resolution of these techniques does not allow us to see activity of specific nuclei or the fine architecture of neural connections that is possible under the microscope in postmortem tissue, but even at this very basic level of brain function, we can begin to image activity that is highly relevant to the peripheral mechanisms that influence medical outcomes.

In the past 20 years, the field of “cognitive neuroscience” has burgeoned (52). Functional brain imaging studies of mental states are being generated at an exponential rate (54). One way of describing this body of research is that it is beginning to define the cortical and subcortical mechanisms of mental states. These imaging studies typically show activity in brain areas that have evolved more recently than the visceral regulatory centers in the brainstem (55). During the course of evolution, cortical (e.g., prefrontal cortex, anterior cingulate cortex, insula) and subcortical (e.g., amygdala, nucleus accumbens, hypothalamus) areas became superimposed on, and took on the role of interacting with and regulating, these
brainstem centers (Figure 2). These same cortical and subcortical areas also contribute to the dysregulation of brainstem centers that occurs in disease states. At the moment, we are beginning to understand the functional cortical and subcortical networks that mediate certain mental and behavioral functions. Much less work has been done on how these neural mechanisms dovetail with and influence autonomic, endocrine, and immune functions. It is precisely in this area that psychosomatic medicine can itself influence the field of neuroscience to promote research in this area by calling attention to its importance.

Perhaps the area of cognitive or affective neuroscience that is most relevant to psychosomatic medicine is emotion and its regulation. The neural substrates of emotion and emotion regulation arguably lie at the foundation of our field, as the field was launched with the publication of *Emotions and Bodily Changes* by Dunbar in 1935 (56). Emotion and its vicissitudes have been central to the field ever since. There is a consensus among researchers that emotions involve a complex pattern of changes in multiple response systems (57,58). Emotions are initiated by an automatic (often nonconscious) assessment of the extent to which needs are met in any given situation and simultaneously involve behavioral, physiological, cognitive, and experiential adjustments to the situation. These changes reset and prepare the organism to act as effectively as possible in the current context. Thus, functionally emotions are action dispositions that interrupt ongoing behavior (59,60) and direct the organism toward a specific goal. From this perspective, emotions have evolved from a more primitive motivational basis that can also be found in more simple organisms. Emotion regulation, in turn, may be defined as automatic and intentional processes that influence what emotions a person has, when they have them, and how they experience and express them (61). Thus, understanding how emotion and emotion regulation are mediated by cortical and subcortical structures has the potential to advance our understanding of how clinically relevant phenomena in psychosomatic medicine influence the regulation of the brainstem centers that, in turn, regulate peripheral physiology and pathophysiology.

The limbic system is a network of structures that participate in generating motivational states and emotional responses. The exact constituents of the limbic system are not widely agreed on because there is no established criterion to determine inclusion or exclusion in this network (62). One popular approach is to define inclusion based on direct connections to the hypothalamus (4), but this approach lacks specificity (62). Nevertheless, despite this lack of consensus, the term continues to be used (e.g., it is an established category at the Annual Meeting of the Society for Neuroscience) because it is a useful code for the neural substrates of motivation and emotion.

The amygdala is a prototypical emotion-related structure at the core of the limbic system (63). Often associated with fear and anxiety (64,65), it plays a wider role in attaching genetically programmed and learned associations to incoming sensory information, therefore giving both positive and negative emotional significance to ongoing events (30,66). The amygdala is essential for aversive conditioning, and it seems to preferentially participate in negative emotional states, perhaps because evolution has endowed us with far more negative than positive emotions. This latter conclusion is based on several lines of evidence including theories of basic emotions that list more negative than positive emotions whether from a neurobiological (67) or a facial expression perspective (68), and evidence that across cultures and languages both younger and older adults know more negative than positive emotion terms (69). Perhaps negative emotions are advantageous relative to positive emotions because they facilitate the response to immediate threats to survival.

The amygdala is therefore critical in the earliest stages of attaching meaningfulness to current events (70). It also participates in orchestrating the somatomotor, visceral, and cognitive responses to this new information by virtue of its connections with other brain structures above and below it in the neocortex. The nucleus accumbens and ventral striatum participate in reward responses and positive emotional states. Other structures that are involved in generating both positive and negative emotional responses include the thalamus, hypothalamus, additional basal ganglia regions, and ventromedial prefrontal cortex. At our present state of knowledge, the neural basis of different emotional states seems to be a function of how these structures work together within a network. The known functions of the structures within this neural network fit well with the concept that emotions involve multiple response systems. There is also some evidence that each basic emotion has its own unique neural architecture (71), although this evidence is mainly derived from animal research (67).

In psychosomatic medicine, we typically measure mental and behavioral states with self-report questionnaires. This means that we rely heavily on that which people can report to us. It is therefore important for psychosomatic researchers to recognize that the vast majority of mental life takes place outside of conscious awareness. The terminology used in this context is to equate conscious processing with “explicit” functions and unconscious processing with “implicit” functions. Gazzaniga, for example, argued that 99% of mental activity does not involve conscious awareness (72). This means that much of the mental activity that influences visceral mechanisms in health and disease may not be captured by self-report inventories. This insight becomes especially important when it is considered that the same distinction between implicit and explicit processes applies to emotion as well as cognition (73).

Current evidence suggests that the structures that generate emotional responses do so in the absence of conscious awareness. For example, the amygdala is thought to influence conscious experience only by transferring its information to other structures in the frontal lobe (62). Recent evidence suggests that feedback from cortical to subcortical structures such as the amygdala is necessary for conscious awareness of emotions to occur (74). Other structures that have evolved more recently than the limbic system seem to participate in conscious experience and conscious awareness. These include...
paralimbic areas, such as the anterior insula, ACC, orbitofrontal cortex, and temporal pole (73).

The posterior insular cortex is the primary projection area for visceral sensation, whereas the anterior insula, particularly on the right side (75), is a higher association area for these bodily signals (76) and is involved in remapping these signals into conscious bodily feelings. The insula is therefore involved in the representation of bodily states that can provide positive or negative biases to cognitive decision-making (71,77). In some ways, the insula functions as a high level "sensory" structure. The phenomenon of somatization, the presentation of emotional distress in the form of somatic complaints (78), is a clinical area of huge importance in psychosomatic medicine and is one in which the insula is likely to play an important role. A recent report by Gündel and colleagues (79) demonstrated greater activity in the insula (as well as other areas) in patients with somatoform pain compared with controls during the experimental induction of pain despite equivalent subjective ratings of pain in the two groups.

The ACC, by contrast, is a "motor" structure situated in the medial (i.e., near the midline) frontal lobe that is highly interconnected with other paralimbic structures, such as the insula, as well as limbic and other subcortical structures. It is a large structure with several divisions (80). The subgenual ACC (Figure 2) is the principal site of autonomic regulation in the frontal lobe and has been labeled the "affective division" of the ACC (81). This structure has important bidirectional connections with the amygdala, periaqueductal gray, nucleus accumbens, hypothalamus, anterior insula, and orbitofrontal cortex, all of which are involved in different aspects of the generation and processing of emotional responses. The rostral (pregenual) ACC (labeled "anterior cingulate cortex" in Figure 2) is just superior to and is closely related to the subgenual ACC, as it has strong bidirectional connections with the amygdala. It is activated in a variety of emotional states and seems to participate both in conscious processing of emotional feeling states as well as performing related cognitive operations, such as thinking about feelings, reflecting on feelings (82,83), and resolving emotional conflicts (84). The mid-cingulate cortex (also called the dorsal ACC), depicted in Figure 2, is predominantly connected to the lateral prefrontal cortex, parietal cortex, and pre- and supplementary motor areas, contributing to its label as the "cognitive division" of the ACC (81). This region plays a major role in the executive control of attention in that its activity increases with any mental effort, particularly when automatic prepotent responses must be suppressed in favor of unrehearsed responses (as in the commonly used Stroop Color-Word Test), and plays a major role in the resolution of conflict (choosing between alternative behavioral response options). This region is highly sensitive to the organism’s state of arousal (85) and participates in registering emotional signals such as pain and the commission of errors that inform behavioral responses and the choice of one action over another (thus suggesting that this region is not purely "cognitive") (86). One simple way of thinking about the ACC is that it is an interface for cognition and affect and is a higher-level brain area where the physiological adjustments are generated that are needed to support cognitive and affective responses.

At a still higher level, the dorsolateral prefrontal cortex, a neocortical structure, is involved in instantiating working memory (87) and setting goals for behavioral responses (30). It is densely connected to the motor cortex and the hippocampus and plays a key role in integrating behavior with existing circumstances in the external environment. By contrast, the medial prefrontal cortex is involved in representing states of the self and monitoring and regulating the internal milieu. This is a higher level of expression of the more general principle that medial brain systems are involved in monitoring and regulating the internal world and elaborating self-generated responses whereas lateral brain systems are more involved in perceiving and responding to the external world (88).

An important principle is that the vertical, hierarchical organization of the brain is such that as one ascends the neuraxis there is a transition from automatic, reflexive responding based on genetic programming to a more flexible, differentiated way of responding based on personal experiences and the unique identity of the individual (again, perhaps in interaction with one’s genetic endowment). It is the paralimbic and neocortical areas that are responsible for mediating the latter. Bottom-up processing of subcortical and bodily emotional information is associated with subsequent top-down inhibition or modulation of those structures that generate emotional responses. Conscious experience emerges from an integration of the two (89). When we think about reportable emotional states and individual differences that are the “bread and butter” of psychosomatic medicine, it is these higher brain structures that are involved in providing a readout/interpretation of what the entire brain and body are doing. Yet, we know that only a limited amount of information reaches that higher level and is reportable. Coming to grips with this reality constitutes a major challenge for psychosomatic medicine and is arguably the area where neuroscience will have its biggest impact on the field.

Neurotransmitter Systems

So far, we have discussed brain function from the standpoint of individual structures, their connection to the other structures, and the emergence of mental events from their interaction within a network. These cognitive and affective functions must be rapidly adjustable to respond to environmental contingencies. Ascending neurotransmitter systems can be thought of as an additional mechanism that has evolved to rapidly alter how the circuits just defined operate as a function of environmental contingencies.

The anatomical regions just described receive extensive dopaminergic, serotonergic, and noradrenergic neuronal projections arising from brainstem nuclei. These ascending systems are crucial regulators of limbic system interactions with prefrontal regions. Individual variation in these regulatory systems are thought to contribute importantly to differences in personality, temperament, and emotional reactivity (90). Indi-
individual variation in personality, stress reactivity, and potential for somatic reactions to stress are thought to be influenced by genetically determined differences in receptor morphology and density or in transporter function in these regulatory systems (90–93).

There are at least three ascending projections of importance for psychosomatic processes. First, the ventral tegmental nuclei of the pons contain dopamine-synthesizing neurons that project to the medial prefrontal cortex, amygdala, cingulate gyrus (including anterior, middle, and posterior cingulate cortices), nucleus accumbens, and the hippocampus, among other areas (94). Release of dopamine in these regions is critical to the appropriate direction of attention to stimuli that signal reward (95) or danger (96), for the motivation of approach behaviors (63), and in regulating working memory (97,98). In parallel fashion, the raphe nuclei of the pons project to these same regions and release serotonin, where they regulate sleep and waking and are closely associated with long-term mood regulation (99) and aggression and affiliation (100). The third system of interest is the noradrenergic system that arises from the locus coeruleus of the pons and that projects to all parts of the central nervous system (101). The noradrenergic system determines the person’s global state of arousal, but it also responds to signals of danger arising from activity of the amygdala and from states of visceral distress signaled in brainstem autonomic sensory nuclei (101). These three systems largely serve to modulate gamma-amino-butyric acid (GABA), which is the primary inhibitory neurotransmitter in the brain, and glutamate, which is the brain’s major excitatory neurotransmitter, along with other neurotransmitters and neuromodulators. There are >50 currently identified neurotransmitter systems reviewed in the literature (102,103).

Genetic Influences on Brain Structure and Function

Advances in brain imaging and genetics in the past two decades make this a felicitous time to join these two fields, in a discipline now being called imaging genetics (104–106). Twin and other genetic study methods indicate strong familial/hereditary influences on structure of the whole brain, and in several specific brain regions (e.g., frontal lobe volume), but less so in others (e.g., “medial brain areas”) (107–109).

Genetic influences on brain function have also been assessed. For example, allelic polymorphism influences have been reported for the relationships between a) apolipoprotein E (associated with Alzheimer’s disease) and differences in memory-task functional activation in the prefrontal cortex and hippocampus (110); b) catechol-o-methyltransferase (involved in dopamine and other catecholamine metabolism) and prefrontal functional responses to a working memory task (111); c) the serotonin transporter and the response of the amygdala to threatening stimuli (112); and d) brain-derived neurotrophic factor with the hippocampus and memory (113).

Genetic influences are very important in brain structure and function. Learning and other environmental factors are essential as well, as are the interactive effects of the two. Such interactive effects are of particular relevance to questions of psychosomatic interest and import.

Information Transfer Systems

The brain interacts with the rest of the organism, largely outside of conscious awareness, through three physiological systems: the ANS, the endocrine system, and the immune system. This interaction is bidirectional: brain to body, and body to brain. Hemispheric laterality of function is important in determining how the brain interacts with these peripheral systems. For example, there are different sympathetic and parasympathetic effects of the right versus left cerebral hemisphere on cardiac action in healthy individuals (114–116) and in people with epilepsy (117–119) or ischemic stroke (120). The ANS and the endocrine systems are primarily responsible for control of the visceral organs and maintenance of homeostasis.

Autonomic Nervous System

There is a growing literature on central and autonomic integration within the context of emotion (121). The ANS (see Figure 3) includes the sympathetic and parasympathetic branches (122,123). There is also an enteric nervous system that controls the gastrointestinal tract (124,125). Whereas the enteric system mainly functions autonomously of the central nervous system (CNS), there are CNS connections that contribute in important ways to its activity. The ANS is a system capable of responding more quickly than the endocrine or immune systems, and the parasympathetic responds more quickly than the sympathetic. The sympathetic and parasympathetic components often, but not always, have antagonistic functions. Both of these systems connect through the spinal cord and several of the cranial nerves to the brainstem, especially the parabrachial nucleus, vagal nuclei (nucleus of the solitary tract [NTS], nucleus ambiguus, dorsal motor nucleus), dorsal raphe, reticular formation (a medially located structure running through the brainstem), and locus coeruleus, to higher centers, especially the thalamus, hypothalamus, amygdala, cingulate cortex, other limbic structures, and several cortical areas including sensory-motor, insular and prefrontal cortices (123,126). The spinal cord, although outside the brain, is part of the CNS. It has information transfer functions (as do certain pathways within the brain itself) and some information processing functions.

In the efferent system, the neurotransmitter for preganglionic (from CNS to ganglion) ANS fibers is acetylcholine. It is also the neurotransmitter for postganglionic (from ganglion to innervated organ) parasympathetic, and sympathetic sudomotor, fibers. The primary postganglionic sympathetic neurotransmitter is norepinephrine. In the afferent system, the logic of “pre” and “post” are reversed. A number of other neurotransmitters including adenosine triphosphate, nitric acid, substance P, calcitonin gene-related peptide, and neuropeptide Y are implicated in the afferent and efferent autonomic systems, and probably an even larger number, including acetylcholine, norepinephrine, GABA, and glutamate, in the CNS systems and structures involved (123,127–132).
In the periphery, afferent viscerosensory receptors are generally of two types: nociceptors and physiological receptors (126,133). Most nociceptors are sympathetic, whereas most physiological receptors are parasympathetic. In the sympathetic system, there are many postganglionic efferent fibers for each preganglionic, commonly but not always producing more diffuse effects than are seen in the parasympathetic system. Additionally, there are several types of specialized recep-

Figure 3. Autonomic nervous system. The sympathetic and parasympathetic divisions of the ANS are depicted in the left and right panels, respectively, and the targets of innervation are schematically depicted in or near the center panel. All brain pathways are schematically depicted. On the left (sympathetic) side, depicted brain pathways include those to the thalamus from the ALS of the spinal cord, output from the thalamus to the neocortex, insula, and amygdala, bidirectional pathways between the hypothalamus and both the amygdala and frontal cortex, output from the hypothalamus to the NTS, and output from the amygdala to the ALS and brainstem. The small bifurcated arrow to the hypothalamus on each side schematically represents the entire set of inputs from cortical and subcortical structures to the hypothalamus. On the right (parasympathetic) side, depicted pathways include those to the thalamus from the NTS, output from the thalamus to the neocortex, insula, and amygdala, and bidirectional pathways between the hypothalamus and amygdala. Roman numerals III, VII, IX, and X (vagus) designate cranial nerves. Three vagal nuclei in the brainstem, including the NTS, nucleus ambiguus and dorsal vagal nucleus, are also depicted. ANS = autonomic nervous system; ALS = anterolateral system; NTS = nucleus tractus solitarius.
tors—baroreceptors, chemoreceptors, osmoreceptors, and thermoreceptors—found in the periphery and/or in the CNS. Afferent fibers predominate in parasympathetic nerves, but are sparser in sympathetic nerves.

After entering specific laminae of the spinal cord, sympathetic afferents ascend primarily in the spinoreticular and anterolateral pathways, through the region of the periaqueductal gray, mainly to the thalamus and hypothalamus (134). From there, connections are made to various (not shown in Figure 3) areas of the cerebral cortex. It has been suggested that, for both ANS and other neural pathways, more lateral pathways are more related to discrete sensory functions, whereas more medial pathways are associated with homeostatic and emotion/motivation-related functions (135).

Afferent parasympathetic pathways include sacral nerves and cranial nerves III, VII, and mainly IX and X. The most important is the vagus (X) with 50% to 80% afferent fibers, carrying thoracic and most of the abdominal visceral afferent impulses. These nerves enter the brainstem and synapse with the NTS, also connecting to the dorsal vagal nucleus, nucleus ambiguous, and parabrachial nucleus, before ascending to the hypothalamus, reticular formation, and other CNS centers (126,134).

The higher one goes in the CNS, the more the distinctions of afferent versus efferent, and sympathetic versus parasympathetic pathways tend to become blurred. Whereas the sympathetic CNS pathways, especially pain-related, are as described above, many other structures and processes are also involved. For example, the NTS is involved in baroreception, processing of pain impulses, and passage of ANS information to higher brain centers via its commissural region (123).

Autonomic outflow from the brain is also complicated, involving many of the structures listed above, and others, sometimes called the central autonomic network (136,137). The hypothalamus is one essential region, especially integrating autonomic and endocrine functions, and including involvement in many reflexive and other functions. Limbic structures are also strongly implicated. Sympathetic outflow from the CNS passes through the sympathetic chain, usually originating from spinal cord levels thoracic 1 to lumbar 2. There is a general somatotopic organization, with higher thoracic segments innervating the head, through lumbar segments to the pelvic viscera (122).

Below the level of the head, parasympathetic efferent impulses to the body pass mainly in the vagus nerve (primarily from the dorsal motor vagal nucleus) and the sacral parasympathetic fibers. Note that the vagus nerve is not part of the CNS (brain and spinal cord). As depicted in Figure 3, structures innervated by sympathetic and parasympathetic efferents include the eye, skin, blood vessels, various glands, heart, lungs, gastrointestinal tract, and other visceral organs (122,123).

Endocrine Function

The endocrine system acts in tandem with the ANS to generate the visceral components of emotions. These endocrine responses serve to act over longer time periods than do the autonomic components, and they tie together the actions of distinct bodily systems in ways that complement the faster and more organ-specific actions of the ANS.
cells, both inhibiting and stimulating their actions (138). This may be one of cortisol’s most direct effects on health. This core HPA response comes under the control of higher brain centers during negative emotional states, such as anger, anxiety, and fear (139–141), and its associated contextual cues, such as novelty and sense of control (142). In this situation, a widespread system of specialized neurons, using CRH as a neurotransmitter, is activated in the prefrontal cortex, limbic system, hypothalamus, and brainstem to coordinate the CNS, endocrine, and autonomic responses during periods of stress (143). These CRH neurons are responsible for the generation of bodily outputs during periods of acute stress. Its long-term activation during states of abnormal emotional activation may accordingly have consequences for bodily function.

Cortisol regulates its own secretion at the hypothalamus by exerting negative feedback on the CRH neurons found there (144). Cortisol also acts at CRH sites outside the hypothalamus to regulate CNS activity during the response to acute and prolonged stress (141,145). These extra-hypothalamic sites include brain structures associated with mood and cognition, including hippocampus, amygdala, nucleus accumbens, and prefrontal cortex (146). Cortisol is notably dysregulated in association with depression (147), and chronically elevated cortisol has been associated with chronic stress (148). Disorders such as Cushing’s disease can contribute to hippocampal atrophy (149–151). Whereas cortisol inhibits neuronal activation at the hippocampus (152), stress levels of cortisol activate the amygdala and sensitize its response to future stressors (153,154). This amygdaloid action of high cortisol levels may potentiate responses to future stress episodes with resulting effects on widespread CNS functions and psychological responses. Although no specific relationships between this sensitization and posttraumatic stress disorder have been proven, such a mechanism seems to be a candidate for future study (155,156). Oxytocin, on the other hand, is known to down-regulate amygdala function and its connection to brainstem effectors in the context of fear-inducing stimuli (157).

The HPA axis is just one example of a hypothalamic-pituitary-endocrine gland system. There are actually six hormones secreted from neuroendocrine cells in the anterior pituitary (thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, growth hormone, and prolactin in addition to ACTH), the secretion of each of which is regulated by specific hypothalamic-releasing hormones, and two hormones released from the posterior pituitary (arginine vasopressin and oxytocin) that are secreted from the axon terminals of neurons that originate in the hypothalamus. Space limitations precluded a more extensive discussion of these other hormone systems. The interested reader is referred to an overview by Cheung and Lustig (158).

**Immune Function**

Over the past 30 to 40 years, substantial support has developed for the existence of bidirectional interactions between the CNS and the immune system, including conditioning of immune responses, immune effects of brain lesions or stimulation, stress effects, and brain changes during immune reactions (159–161). As depicted in Figure 5, on the efferent (output) side, the influence of the brain on the immune system is mediated through the peripheral ANS and endocrine mechanisms, whereas on the afferent (input) side, the influence of the immune system on the brain is direct via soluble cytokines as well as indirect through the vagus nerve (161). Nervous system factors (162) include hemispheric asymmetry (163), HPA, adrenergic, neuropeptide, and serotonergic substances (159), and various psychological factors (164). Implicated nervous system regions include many of those noted above: afferent and efferent vagal pathways, several brainstem structures (medulla, reticular formation, raphe, parabrachial nucleus, and NTS), limbic-related structures (amygdala, nucleus accumbens, hypothalamus, hippocampus), and medial frontal cortex (162). A critical frontier for psychosomatic medicine is to add greater precision to the anatomy and physiology of brain-immune interactions in the decades ahead. Recent work by Ohira et al. and Matsunaga and colleagues (165,166), in which brain imaging, immune, endocrine, and autonomic parameters are measured simultaneously, suggests that our understanding of brain-immune interactions is likely to advance in the near future.

Ader (167) demonstrated conditioned immunity 30 years ago. Earlier Pavlovian conditioning studies suggested that this could occur (168). Both ANS and endocrine mechanisms are involved, one of many examples that these systems can interact. Changes in natural killer cells (NKC) and the cytokine interleukin-1 are examples of immune system components susceptible to conditioning (169,170).

Stress can affect immune status, especially NKC (164,171–174). This change in NKC was associated with changes in ANS function, including heart rate (172,173), blood pressure (172), and catecholamine (and other circulating) substances (174). Cytokines can also be influenced by stress (175,176). Adrenergic mechanisms are implicated in stress-induced cytokine changes (176,177). One twin study (178) indicated that both genetic and environmental factors influence immune-related stress reactivity.

Immune changes have been studied in several psychiatric (i.e., brain) disorders, especially depression (15). Changes in NKC activity have been reported (179,180), as have changes in various circulating cytokines (181–183). Cytokines can cross the blood-brain barrier, and can affect central monoaminergic neurotransmitters and HPA axis function (184–186). Administration of immune-active substances can produce “sickness behavior,” symptomatically similar to depression (175,184–191). Psychologically related changes in immune function have also been recognized in various medical conditions, including human immunodeficiency virus (HIV) infection, cancer, and cardiovascular disease (164,192,193).

**CONCLUSION**

This review illustrates that enormous progress has been made in understanding how the mental states relevant to psychosomatic medicine are instantiated in the brain. A host of methods are now available to study the brain in humans, each of which have their own unique profile of advantages and
disadvantages. The pathways through which the brain interacts with end organs in a bidirectional manner are beginning to be delineated. As investigators in psychosomatic medicine, we can enrich our theoretical models and empirical investigations by including further consideration of the brain. Largely separate bodies of literature have linked mental states (A) to the brain (B), information transfer systems (C), and the body proper or disease (D). It is only by crossing these four levels of analysis that we can fully integrate these bodies of knowledge and further elucidate critical “mind-body interactions.” By applying the empirical findings and methods emanating from the field of neuroscience, we can begin to come closer to answering questions regarding the biological mechanisms whereby psychological, behavioral, and social factors can promote health or disease. In the companion paper (12), we next consider the current state of knowledge regarding brain mechanisms that may be relevant to cardiovascular disease, functional gastrointestinal disorders, pain, and placebo and we consider the implications of bringing the brain back into mind-body medicine for future research and clinical practice.

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Figure 5. Brain-immune system interactions. The brain regulates the immune system through the autonomic and neuroendocrine systems. The figure depicts sympathetic innervation of the adrenal medulla, which secretes epinephrine, and both sympathetic and parasympathetic innervation of lymph nodes. Neural connections between the hypothalamus, brainstem nuclei, and autonomic ganglia are not shown. Neuroendocrine influences that alter immune function and that emanate from the hypothalamus consist of the hypothalamic pituitary axis, prolactin, and growth hormone which, together with epinephrine, influence innate and adaptive immune cells that secrete cytokines. In addition to autonomic feedback, several different types of cytokines feed back to multiple brain sites that are not depicted in this figure. IL = interleukin. Adapted from the original and printed with permission from Macmillan Publishers Ltd; Nature Reviews Immunology, Glaser R and Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. 2005;5:243–51.
illustrations (Figures 2–5). We also acknowledge the financial support for the creation and reproduction of the illustrations from the National Center for Complementary and Alternative Medicine, NIH, the Office of Behavioral and Social Science Research, NIH, and the American Psychosomatic Society. We also thank neuroanatomist John Nolte, PhD, who consulted on the illustrations and Ahmad Hariri, PhD, who consulted on the “imaging genetics” section.

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