The Rebirth of Neuroscience in Psychosomatic Medicine, Part II: Clinical Applications and Implications for Research

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During the second half of the last century, biopsychosocial research in psychosomatic medicine largely ignored the brain. Neuroscience has started to make a comeback in psychosomatic medicine research and promises to advance the field in important ways. In this paper we briefly review select brain imaging research findings in psychosomatic medicine in four key areas: cardiovascular regulation, visceral pain in the context of functional gastrointestinal disorders, acute and chronic somatic pain and placebo. In each area, there is a growing literature that is beginning to define a network of brain areas that participate in the functions in question. Evidence to date suggests that cortical and subcortical areas that are involved in emotion and emotion regulation play an important role in each domain. Neuroscientific research is therefore validating findings from previous psychosomatic research and has the potential to extend knowledge by delineating the biological mechanisms that link mind and body more completely and with greater specificity. We conclude with a discussion of the implications of this work for how research in psychosomatic medicine is conducted, the ways in which neuroscientific advances can lead to new clinical applications in psychosomatic contexts, the implications of this work for the field of medicine more generally, and the priorities for research in the next 5 to 10 years. **Key words:** neuroscience, anterior cingulate cortex, emotion, pain, cardiovascular regulation, placebo.

ACC = anterior cingulate cortex; **aMCC** = anterior midcingulate cortex; **CAD** = coronary artery disease; **CVD** = cardiovascular diseases; **DBS** = deep brain stimulation; **DLPFC** = dorsolateral prefrontal cortex; **ECG** = electrocardiographic; **FGID** = functional gastrointestinal disorder; **fMRI** = functional magnetic resonance imaging; **IBS** = irritable bowel syndrome; **MCC** = midcingulate cortex; **MEG** = magnetoencephalography; **MPFC** = medial prefrontal cortex; **NAC** = nucleus accumbens; **OFC** = orbitofrontal (or orbital prefrontal) cortex; **pACC** = pregenual anterior cingulate cortex; **PAG** = periacqueductal gray; **PET** = positron emission tomography; **PCC** = posterior cingulate cortex; **PI-IBS** = post infectious irritable bowel syndrome; **S1** = primary somatosensory cortex; **S2** = secondary somatosensory cortex; **sACC** = subgenual anterior cingulate cortex; **sTMS** = slow transcranial magnetic stimulation; **TMS** = transcranial magnetic stimulation; **VNS** = vagus nerve stimulation.

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INTRODUCTION

One of the primary goals of research in psychosomatic medicine is to delineate the biological mechanisms whereby psychological, behavioral, and social factors influence disease outcomes, and to use this information in the service of optimizing medical care. In the prior paper in this two-part series (1), we argued that applying current methods in human neuroscientific investigation in psychosomatic research would greatly enhance our ability to identify causal mechanisms that underlie mind-body linkages to disease pathogenesis. We now provide an overview of the current state of knowledge about the relations of brain function to select organ systems (cardiovascular, gastrointestinal) and clinical contexts (pain, placebo responses).

Much of the functional brain imaging literature to date has focused on understanding the neural basis of mental states from a systems neuroscience perspective. As noted in our prior paper, knowledge is expanding rapidly with respect to how the brain executes a variety of cognitive, emotional, and social functions and their interrelations (2–4). There has also been considerable attention to the role of brain dysfunction in neurological and psychiatric disorders, treatment effects, and recovery processes including neuroplasticity (5). Given that functional magnetic resonance imaging (fMRI) was first reported in humans in 1992 (6), there has been an astounding record of progress in a short period of time (7). This work constitutes an outstanding foundation for "brain-body" research because we are now able to study how different mental processes are instantiated in the brain. There is the potential to integrate these advances with our established skill in studying the three critical information transfer systems—autonomic, endocrine, and immune—that are thought to link brain and body as well as end-organ function and relevant medical outcomes (1). Thus, the components are now in place to enable the field of brain-body research to take off.

In this paper, we provide selective reviews of research that link the brain to clinically relevant phenomena in psychoso-

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matic medicine to illustrate important applications of neuroscience in our field. In each section, we note the levels of analysis discussed in the companion manuscript: A = mind, behavior; B = brain; C = information transfer systems (autonomic, neuroendocrine, immune); and D = end organ (e.g., heart). The first section examines the use of neuroscientific methods in studying the cardiovascular system. The second section addresses functional brain imaging studies in patients with functional gastrointestinal disorders (FGID) and associated visceral (internal organ) pain. In section three, we examine the brain bases of acute and chronic somatic (musculoskeletal) pain. In section four, we briefly review functional brain imaging studies of placebo in relation to pain. Each of these sections reflects a long-held belief, since the inception of modern psychosomatic research, that emotion is central to an understanding of mind-body relations (8–10). In the final section, we discuss the implications of this work for how research in psychosomatic medicine is conducted, clinical applications, implications for the field of medicine more generally, and the priorities for research in the next 5 to 10 years.

Cardiovascular Diseases (CVD)

CVD comprise the leading causes of morbidity and mortality in most westernized countries and are a major concern for developing economies (11–13). There is a primacy to the control of cardiovascular physiology because the functional integrity of all bodily organs depends on an adequate supply of blood. Cardiovascular function is exquisitely sensitive to emotional, societal, and environmental challenges. Habitual or intense patterns of behavioral (psychological and physical) challenge can under certain circumstances undermine cardiovascular health (14), perhaps in part via repeated, behaviorally-evoked cardiovascular perturbations.

To understand the neural mechanisms through which environmental and psychological factors influence the integrity of the human cardiovascular system, one can describe the brain centers activated during concomitant changes in cardiovascular state. In that regard, simple respiratory, exercise, and cold pressor challenges that elicit acute increases in heart rate and blood pressure are associated with changes in activity within cortical (insula, cingulate, and medial prefrontal cortices) and subcortical (thalamus, midbrain, pons) regions measured by fMRI (15,16). During cognitive and physical effort, the magnitude of evoked cardiovascular arousal, including increased heart rate or blood pressure, correlates with regional neural activity within the forebrain (insula, pregenual anterior cingulate cortex (pACC), and anterior midcingulate cortex (aMCC)) and brainstem (dorsal pons) regions (17–20). Activity within some of these regions also predicts beat-by-beat changes in sympathetic (low-frequency) influences on heart rate (21).

In these studies, the psychological challenges have included difficult arithmetic, working memory, or Stroop tasks. More potent emotional challenges, including threat of an aversive event, also engage activity within the amygdala. Neuroimaging studies have linked amygdala activity to emotion-induced changes in cardiovascular responses (22), which may be driven by sympathetic (21,23) or parasympathetic activation (17,24). A striking example is the predictive relation of amygdala activity to cardiac contractility (measured using cardiac imaging) in the context of anxiety (25). Reflecting the distinct contributions of the sympathetic and parasympathetic autonomic axes to cardiovascular control (and their differential contributions to cardiovascular morbidity), neuroimaging studies have further suggested a neuroanatomical segregation in behaviorally integrated control, even at the level of the cerebral cortex. Thus, activity within ventral frontal regions—including the pACC, which corresponds to the area labeled "ACC" in Figure 1a and 1b (26), the subgenual cingulate (sACC) and medial orbitofrontal cortices—is linked to parasympathetic influences on the heart measured by heart rate variability (24,27,28). From the standpoint of the A-B-C-D framework introduced in the companion manuscript, these studies simultaneously address levels A (psychological, behavioral), B (brain), and C (information transfer system, specifically the autonomic nervous system).

Such studies of healthy individuals help to define the neural mechanisms that translate emotional challenges into adaptive or maladaptive cardiovascular reactions. Similar insights may be gained from studies of stress-induced humoral responses, which have known effects on the heart and blood vessels. Enhanced cardiovascular responses to stress may constitute a psychophysiological predictor of cardiac morbidity and mortality (29–31). Among healthy individuals, activation within the posterior cingulate cortex (PCC) predicts individual differences in cardiovascular responsivity, hence, by inference, cardiac risk (20,24). Among those with CVD, a more distributed enhancement of neural responses to stress is associated with vulnerability to ischemia and arrhythmia (32). The latter studies, which did not include mediating mechanisms between brain (B) and heart (D), constitutes an A-B-D approach.

Cardiac risk is also enhanced by psychosocial conditions, including grief, depression, personality, and socioeconomic factors (A-D) (14,33). Low vagal (parasympathetic) tone and exaggerated stress-induced sympathetic (blood pressure and heart rate) responses combine as potential physiological mediators linking psychosocial factors to cardiac risk (23,34,35). Functional abnormalities within the sACC are observed in at-risk recently bereaved individuals and seem to correspond to withdrawal of the protective parasympathetic vagal influence on heart function (36). The sACC and ventromedial prefrontal dysfunction are also commonly reported in depressed patients who also manifest similar predisposing attenuation of parasympathetic tone (36). Interestingly, the structural morphology of these brain regions in healthy individuals relates to social predictors of cardiac risk, including perceived life stress and social standing (37,38).

Abnormal and exaggerated activity within discrete brain regions (39,40), particularly during emotional stress, may trigger potentially fatal arrhythmic cardiac events (41). The presence of preexisting heart disease greatly increases this

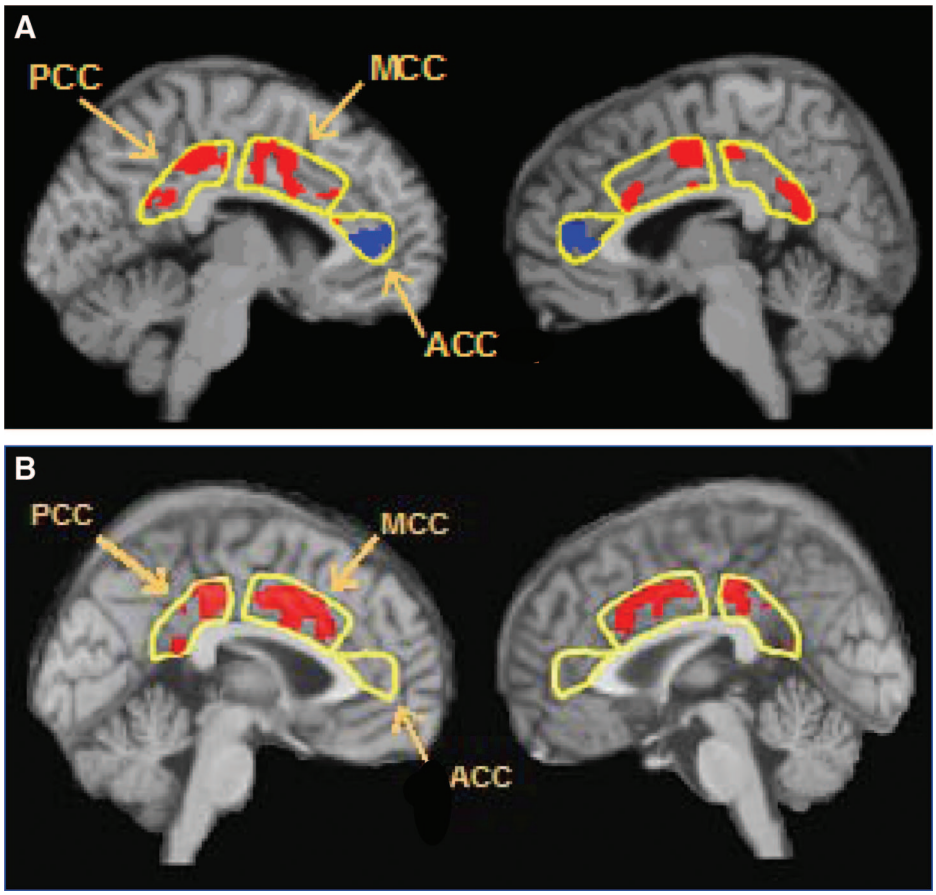

Figure 1. **A**. Response to painful (50 mm Hg) distensions grouped for patients with a history of IBS and abuse compared with a combined group of patients with only IBS, only abuse history and controls. Greater activation (depicted in red) is seen for the IBS and abuse group compared with the others in the left MCC and left PCC with less activation (depicted in blue) in the left and right ACC. **B**. A positive correlation between all subjects' pain reports during 50 mm Hg rectal distention and activation of the MCC and adjacent PCC. The correlation was significant in the left MCC. This finding links the association of greater pain reporting with rectal distension to increased MCC and PCC activation. ACC = anterior cingulate cortex; IBS = irritable bowel syndrome; MCC = midcingulate cortex; PCC = posterior cingulate cortex. Reprinted with permission from the American Gastroenterological Association Copyright 2008; Ringel Y, et al. Effect of abuse history on pain reports and brain responses to aversive visceral stimulation: an fMRI study. Gastroenterology 2008; 134: 396–404; see (26).

risk. Lane and Schwartz (42) proposed that the lateralization of efferent autonomic drive from the brain may be a mediating factor. Lateralized hemispheric dominance of brain responses to powerful emotional challenges may evoke lateralization of sympathetic outflow to the heart, affecting the spatial pattern of myocardial repolarization. If the electrical initiation of contraction reaches regions of the heart muscle before they are fully repolarized, the sequential coordination of contraction is disrupted, a process already destabilized in cardiac disease. Proarrhythmic changes in myocardial repolarization can be quantified from the morphology of electrocardiographic (ECG) T waves across chest leads. The autonomic responses to mental stress shifts the heart toward a proarrhythmic state, even in healthy people (an A-D approach) (43). In a positron emission tomography (PET) brain imaging study of cardiac patients, right-sided midbrain activity (in the region of the parabrachial nucleus) during mental and physical challenges predicted proarrhythmic myocardial changes and identified those patients at greatest risk of arrhythmia (44). A further electroencephalographic study in patients with preexisting heart disease, using similar challenges, suggests that such lateralization of stress-related brain response may be a consequence of a lateral dominance of a cardio-cerebro-cardiac loop governing cardiac contractility (45). Although this line of research includes all four elements of the A-B-C-D approach, specific studies that included measures of end-organ function, such as myocardial electrical instability, have not included the autonomic and neuroendocrine (level C) mediating mechanisms.

Ischemic changes in the heart are associated with alterations in brain activation that may promote central arrhythmogenesis. This has been noted among persons with silent myocardial ischemia or angina pectoris. For example, Rosen and colleagues (46) showed in cardiac patients that ECG evidence of ischemia after dobutamine infusion evoked enhanced subcortical brain responses. Similar subcortical responses extended to involve many cortical centers when the patients experienced anginal chest pain. Interestingly, there were decreases in aMCC activity in association with anginal chest pain. Soufer and colleagues (32) also showed pACC and posterior MCC deactivation and shifts in the symmetry of brain activity in patients who developed (silent) myocardial ischemia during mental stress challenge. Further studies (47)

highlighted the enhancement of right anterior insula activity during patients' experience of cardiac chest pain in cardiac syndrome X.

In healthy subjects, neural afferent signals from the heart to the brain may enhance emotional experience. Further, individual differences in "interoceptive" perceptual awareness of the heart, measured using heartbeat detection tasks, can predict patterns of emotional responsivity (48). Neuroimaging studies show that accurate detection of heart beat timing is associated with increased activity in the right anterior insula (49) and related regions of the aMCC (50). Importantly for psychosomatic medicine, individual differences in interoceptive awareness measured using heartbeat detection tasks also predict day-to-day anxiety symptoms (51), cardiac focus in heart patients, and more general sensitivity and "pathologization" of bodily sensations (49). These important studies represent an A-B-C approach.

Brain structure and function, and their behavioral output, are also directly affected by the heart (a D-B-A approach). CVD, including hypertension, cardiac arrhythmias, cardiac arrest, myocardial infarction, heart failure, and peripheral arterial disease, have a negative impact on cognitive function, even before stroke or dementia (52). Virtually all types of perceptual-motor and cognitive function can be affected, although executive functions, motor functions, and memory may be most vulnerable. Typically, the degree of cognitive impairment may increase with the severity of CVD (53). Relevant structural brain mechanisms include increased white matter disease, silent brain infarction, brain atrophy, and atherosclerosis of the large cerebral and cervico-cerebral arteries. Possible functional brain mechanisms include reduced cerebral perfusion or metabolism, particularly in fronto-temporal, subcortical, and border zone regions, altered brain activation patterns, endothelial dysfunction, neurotransmitter disturbance, cellular dysfunction, and alterations of the blood-brain barrier (52,54). Interestingly, enhanced cardiovascular reactivity to laboratory-based psychological challenges accompanies diminished cognitive function (55) and is linked to the presence of silent cerebrovascular disease (56) (a C-B-A approach). It also is predictive of stroke (57) and progression of carotid atherosclerosis (30,58).

Alterations in brain and cognitive function associated with CVD may have important potential implications for psychosomatic medicine. First, decrements in cognitive function can negatively affect an individual's quality of life in the realms of mood and motivation, social and occupational behaviors, and daily living skills. Second, cerebral involvement influences the effectiveness of pharmacological interventions and adherence to other treatments by affecting organization, motivation, and often management complexity. Third, changes in brain structure and function may accelerate physical decline and promote the progression of incidental disease through impact on complex communication between brain and periphery with negative influence on sympathetic outflow, neuroendocine and immune function, and ultimately on behavioral or lifestyle factors that can influence disease progression.

Functional Gastrointestinal Disorders

FGID affect a large proportion of the population in the US. The most common conditions studied include irritable bowel syndrome (IBS) occurring in about 10% of the population, functional dyspepsia affecting another 3% to 5% of the population, and a variety of other disorders from esophagus to anorectum (59). Most of the work in brain imaging has been done in IBS, a disorder characterized by abdominal pain or discomfort associated with bowel disturbance (diarrhea and/or constipation). The pathophysiology of these disorders is multifactorial and relates to abnormal motility, visceral hypersensitivity, altered bacterial flora, and dysregulation of the brain-gut axis (60). These disorders therefore are amenable to study at the level of the brain because it provides a "window" into understanding the relations of stress and altered mood with disturbed gastrointestinal function. Accordingly, recent research in brain-gut interactions has used brain imaging technology (61) to identify the structure and function of regions of the brain that are associated with visceral pain perception, stress, and other psychosocial variables within the context of FGID. Neuroimaging modalities may have diagnostic potential, and possibly even therapeutic application, particularly with regard to understanding the benefit of centrally targeted modalities like antidepressants and psychological treatments for FGID. The following provides support for this supposition (62).

Stress has been associated with the development of certain FGID, such as post infectious irritable bowel syndrome (PI-IBS)—the persistence of functional GI symptoms for several months after a bacterial infection. From the standpoint of the A-B-C-D framework, this finding exemplifies an A-D approach. PI-IBS is not only associated with increased inflammation in the gut mucosa but also with the presence of increased psychological distress at the time of initial infection (63,64). Thus, it was posited that relative to post infectious controls, central nervous system amplification (due to stress) of peripheral signals in the psychologically distressed group may increase the perception and perpetuation of symptoms, thus leading to the development of PI-IBS (65). More recently, it was found that among women having abdominal surgery for nonpainful gynecological conditions, up to 17% developed abdominal pain at 3 and 12 months and 3% developed IBS; this was significantly greater than the matched nonsurgical group. More importantly, predictors of the development of pain were not related to factors associated with pelvic trauma (e.g., injury, bleeding, infection, length of surgery) but rather to premorbid psychosocial factors, such as belief that the surgery would not go well, low sense of coherence, and a low sense of control (66). These findings lend support to the notion that the development of functional GI symptoms is strongly related to premorbid psychosocial influences, and these factors are amenable to brain imaging investigation.

It is well recognized that patients with FGID have greater gut reactivity to various stressors than those without FGID. This is manifest as increased motility and visceral sensitivity

to a variety of stressful stimuli including meals, visceral distension, physical activity, hormonal changes, and psychological stress (67,68). Conversely, visceral activity has central representation (reflecting a D-A approach); for example, distending the colon activates the locus coeruleus, and this may explain the high degree of anxiety seen in patients with visceral pain. This bidirectional association is a demonstration of the "brain-gut" axis.

The brain-gut axis is "wired" to modulate visceral afferent painful signals and responses to stress. Amplification of visceral signals occurs at the level of the mucosa via sensitization from inflammation or injury, at the dorsal horn (central sensitization) or at midbrain structures (67). Furthermore, corticofugal pathways can amplify or suppress afferent signals from the gut. These descending pain systems, in addition to neuroendocrine (e.g., hypothalamic-pituitary-adrenal axis), cognitive-attentional and autonomic control loci, are closely integrated and may mediate stress responses (69). Undifferentiated multimodal responses occur to a greater degree in patients with FGID who show increased motor, sensory, and autonomic reactivity via these central modulatory systems (69).

Specific areas of the cortico-limbic modulatory system regulate visceral pain and emotional responses. A consensus is emerging that visceral signals can activate regions associated with unpleasant affective and autonomic responses, whereas somatic signals activate regions associated with skeletomotor responses and spatial orientation (70,71). Specifically, visceral stimulation activates cortico-limbic modulatory systems including the insular cortex, the medial thalamus, the right ventrolateral prefrontal cortex, and the anterior cingulate cortex (ACC) (reflecting a D-B approach). As noted in the companion manuscript (1), the cingulate cortex consists of structurally and functionally heterogeneous regions (72,73) and is of particular interest with regard to pain regulation and stress response in the FGID. This area processes information on stimulus intensity, emotion, mood, and attention, and is also involved with unpleasant emotion and autonomic responses. It consists of an anterior portion, the pACC and a more dorsal and caudal portion in the middle of the cingulate gyrus, the midcingulate cortex (MCC) (also called the dorsal ACC). The pACC, specifically the supragenual portion, is linked to emotion such as happiness and sadness. It is also rich in diprenorphine, an endogenous opioid (74), as well as high concentrations of opioid receptors (75). Activation of this region may initiate descending pain inhibition pathways. The aMCC is associated with attentional processes, decision-making (response selection) and premotor activities in response to visceral events that require a recoding of behavior (73). Recent data suggested that activation of the aMCC with visceral pain is associated with high levels of fear (73). Thus, with painful visceral stimulation, there may be an increase in activity of the pACC associated with emotional distress and an increase in activity of the aMCC where pain is coupled with fear, increased attention to the stimulus, and inhibition of motor activity (response selection) (76). From the standpoint of the A-B-C-D framework, this line of research reflects a D-B-A approach. In general, studies of the brain-gut axis have not included level C variables.

Functional brain imaging demonstrates differences in central pain modulatory systems between patients with IBS and controls. PET and fMRI, the most commonly used techniques in the FGID, provide a window to increases (activation) or decreases (deactivation) in brain function. With IBS, this is usually done with rectal distension to provide a painful afferent signal that registers a response in the brain. Several published studies indicated differences between patients with IBS and healthy individuals in levels of activation of these cortico-limbic pain modulatory systems. Despite inconsistencies across the studies, in general, there is an association of ACC activation to rectal distension in IBS relative to controls (61). Studies using both fMRI and PET have shown increases in activity of unspecified areas of the ACC relative to controls (77). Others showed increased activity of the aMCC (70,78–81) or pACC (82) relative to controls, thus linking emotion or fear with visceral pain in these patients. Still others showed increased pACC activity in controls relative to IBS (83,84). Some of these studies reported an expected correlation between aMCC activation and greater pain reports to rectal distension that was amplified by psychosocial distress (79,26). Again, these studies reflect a D-B-A approach.

The field of brain imaging in the FGID is not developed enough to provide complete information regarding the localization of regional brain activation in the FGID and their relation to stress, pain, and emotion. Although it is difficult to obtain a consensus as to which brain subregions show increased or decreased activity (61), the emerging data suggest that increased activation of the aMCC is a noxious response to visceral stimulation appearing more in patients with IBS, and which is enabled by psychosocial distress (a D-B-A approach). Possibly decreased activation of the pACC is associated with downregulation of visceral afferent input. Thus, differences between patients with IBS and controls do exist and topographical mapping of the regions of activation is an area for future study.

The brain areas of interest in the FGID are also areas linked to and activated by stress. Similar to brain imaging research within psychiatry that relates activation of the ACC and related limbic structures to psychosocial disturbances (85–88), preliminary data with IBS patients show that ACC activation to rectal distension correlates with anxiety (89), stressful life events, maladaptive coping (90), and a history of abuse (79,83,26) (a D-B-A approach). Furthermore, abuse history and IBS diagnosis seem to have synergistic effects associated with even greater activation of the aMCC. In a recent study (Figure 1), patients with a history of abuse with IBS had significantly greater activation of the MCC and deactivation of the pACC, which correlated with the level of pain experienced during rectal distension (a D-B-A approach) (26). These studies are providing links among psychological distress, IBS, and greater pain reporting.

Brain imaging may permit targeting of susceptible groups to central treatments in the FGID. Brain imaging may help

clarify the action of psychological treatments and antidepressants, and possibly monitor and predict their effects. One case report showed that clinical improvement in IBS associated with antidepressants and counseling occurred with a reduction in symptom reports, visceral pain threshold, and aMCC activity (79). A study of cognitive behavioral treatment showed that, when compared with pretreatment values, IBS patients had significant reductions in symptom severity, anxiety, and pACC activity (91), and another study showed reduced stress-related activation of the pACC among patients treated with amitriptyline (92).

These observations have been tantalizing but to date have not contributed to a coherent understanding of how, specifically, the brain contributes to FGID. This is where an integration of psychosocial research with brain science may be useful in formulating new and testable psychosomatic hypotheses, and to date these studies are only beginning. One of the striking observations in this field is that at least 40% of patients with IBS as well as other functional somatic syndromes have a history of sexual abuse, and abuse is associated with more clinically complicated and disabling IBS (93). Given that sexual abuse may be associated with impairments in the processing of emotional distress (94), it could be that when emotional distress about current life issues occurs in patients who have been abused, the emotion gets processed in a less differentiated way corresponding to brain processing that is more subcortical than cortical (10). Subcortical interactions between pain and emotion may then occur that influence what information gets transmitted for conscious processing. The latter may result in pain suffused with emotion, which would be associated with greater suffering, in contrast to pain and emotion "reporting" independently to the cortex, which would be a more adaptive pattern associated with less suffering. Such a pattern has been difficult to detect because doing so will require disentangling state emotional responses, trait emotional characteristics, pain thresholds, and pain responses using a broader array of stimuli to probe brain function than rectal stimulation alone. The field will surely advance by using the results of such studies to inform the design of translational research that will ultimately benefit patients.

Acute and Chronic Somatic Pain

For most people and for most of the time, pain is a symptom of disease rather than a disease in its own right. In the A-B-C-D framework used for this review, pain usually follows dysfunction in the body proper (level D) that subsequently causes a cascade of changes in information transfer systems (level C) and the brain (level B) with the resultant experience of pain (level A). Fixing the dysfunction in the body (level D) usually resolves the problems in C-B-A and so the pain goes away.

During the course of the past 15 years, there have been considerable advances made in our understanding of what happens in the brain (level B) when there is an experience of pain (level A) caused by a noxious stimulus delivered to the body (level D). This progress is largely due to the use of functional imaging technologies that allow direct examination of brain activity during a variety of sensory experiences including pain (95–99). The first papers examining brain responses to noxious somatic stimuli debated the relative importance of the "lateral" and "medial" pain systems. Lateral spinothalamic pathways transmit information to the primary sensory cortex (S1), which is believed to code for the intensity, duration, and location of noxious stimuli. Medial spinothalamic pathways transmit information to the limbic cortices, including the ACC, which are believed to code the motivational and affective qualities associated with noxious stimulation. Since that time, there has been an exponential rise in the number of functional imaging studies using noxious stimulation and these studies have been extensively reviewed (100,101).

Figure 2 summarizes reported activations on the lateral (top) and medial (bottom) surface of the brain. Each circle represents the reported coordinates from various pain studies (100). Figure 2 illustrates that pain experience results in widespread lateral cortical activity encompassing areas traditionally associated with sensory processing (S1 and secondary somatosensory cortex, S2) as well as areas associated with cognition and the organization of behavior (prefrontal cortices). There is evident lateralization of responses in the primary sensory cortex, which is consistent with the presumed role of localization and the known anatomy. Figure 1 also illustrates widespread activation on the medial surface with evident activation of the MCC midcingulate region (101). The MCC connects to the dorsolateral prefrontal and motor cortices and is believed to be predominantly involved in the organization of behaviors to minimize stress or conflict. Intriguingly, there is evidence of laterality with left-sided noxious stimulation showing an evident bias toward the right MCC and right-sided noxious stimulation bias toward the left MCC. Although the usual interpretation of MCC activity includes emotion, a lateralized pattern clearly suggests that some sensory coding may also be occurring.

In summary, a variety of functional imaging studies with somatic noxious stimuli have demonstrated reasonably consistent activation of S1, S2, MCC, and the prefrontal cortex. Straightforward views of pain as a simple sensory response to a noxious event were undermined by these widespread activations. Functional imaging revealed the brain mechanisms of pain (level B) to be more complex than originally envisaged and these findings were integrated into a broad psychological view of pain (level A) as a complex, multidimensional experience involving sensory, affective, and cognitive components. More recently, functional imaging data with acute pain have been integrated into the generally accepted description of pain as a biopsychosocial phenomenon (102–104).

This understanding of pain is not merely academic—it suggests that pain can be experienced as a symptom or disorder in its own right and independently of injury or threats to tissue. This understanding renders the relation between activity in the body and brain (levels B-C-D) and the experience of pain (level A) much more vexed but also provides the oppor-

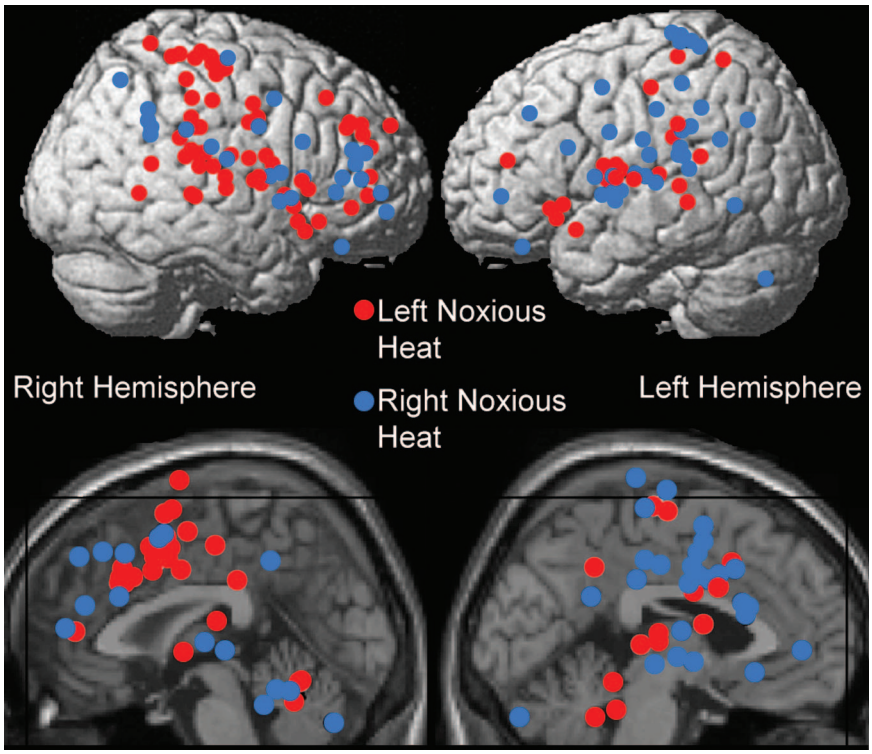

Figure 2. Lateral (top) and medial (bottom) surface activation during painful experience induced with noxious heat. The center of each reported regional cerebral blood flow increase is shown when noxious heat was delivered to the right side of the body (blue circles) and to the left side of the body (red circles).

tunity to understand various chronic pain disorders where pain exists without obvious objective disease and beyond the point of any useful protective purpose.

Individuals who present with symptoms of pain for ≥6 months are described as suffering from chronic pain. Prevalent diseases associated with chronic somatic pain include cancer, arthritis, and diabetes, and chronic neuropathic pain can follow accidental or surgical damage. But there are also many somatic pain syndromes that do not have any obvious precipitating cause or disease process to explain the pain. These latter patients are described as suffering chronic functional pain and include fibromyalgia, idiopathic facial pain, and nonspecific low back pain. Chronic somatic pain is common in the general population with prevalence estimates ranging from 10% to 55% (105). Chronic pain considerably reduces quality of life and there is evidence that chronic pain increases mortality independent of any disease that may cause the pain (106). Further, chronic somatic pain generates considerable healthcare costs and decrease work-related productivity. Nonspecific low back pain, for example, is estimated to result in annual losses of 149 million work-days (107).

Regardless of what may cause chronic somatic pain, conventional medical therapy has a limited efficacy in treating the pain. On average, drug treatments provide about 30% greater pain relief than placebos, which is partly due to the surprising strength of placebo responses but also partly due to the surprising weakness of drug intervention. A combined therapeutic response to chronic pain is not unusual, often involving patients consuming a cocktail of analgesic medicines and attending various behavioral therapeutic sessions, in an effort to minimize pain experience. Unfortunately, even a combined therapeutic approach often fails to deliver any consistent benefit (108).

The persistence and apparent intractability of chronic somatic pain has led to an increasing interest in the possibility of central changes and the use of functional imaging to examine the brain mechanisms underlying somatic pain. The premise of such studies is the presumed relationship between the brain (level B) and pain (level A) that is generally described, but not explained, under the rubric of the biopsychosocial model (109,110).

The biopsychosocial approach to pain is based on several propositions, the central one being that an individual's emotions and behavioral activity in response to an event are influenced by their appraisal of that event and environmental circumstances. Thus, in addition to the biology of a noxious event, the biopsychosocial model introduces psychological and social factors that may mitigate or enhance the final experience of pain. Crucially, the biopsychosocial model places an emphasis on the content of pain experience rather than on the source of noxious information. Pain is thus regarded as a conscious experience that may be modulated by mental, emotional, and sensory mechanisms and includes both sensory and emotional components.

The biopsychosocial concept integrates the key findings of the past 50 years of research, namely, that the relation between pain and injury is variable; pain may persist or occur in the absence of injury; pain is not a single sensation but has many

dimensions; there is no adequate treatment for many types of pain; there are multiple ascending pathways that can carry pain information to the brain; and there are multiple areas of the brain that process pain information. The biopsychosocial understanding of pain has been particularly valuable in helping to understand the persistent and intractable nature of chronic somatic pain. Known relations between somatic sensation, catastrophic thinking, negative affect, and pain have led to suggestions that various stimuli ranging from injury elsewhere in the body to emotional and cognitive inputs from higher neural centers can expand, amplify, or create chronic pain symptoms.

Studies have, for example, revealed augmented activation in patients with fibromyalgia and low back pain to mechanical noxious stimulation (111,112). Gracely's group has also demonstrated greater MCC responses in patients with high levels of catastrophic thoughts about pain (113). This latter finding ties dysfunctional pain thoughts (level A) to greater pain experience through the MCC (level B), which is a critical integrative pain region (101). Other B-A links have also been made, such as augmented pACC responses associated with pain experience during heat allodynia (114).

The ACC as a whole has long been considered a component of the limbic (emotional) brain (115–117) and has been implicated in the maintenance of chronic pain (101). The MCC contains nociceptive neurons and projects directly to motor regions whereas the pACC contains a high density of opioid receptors and projects directly to affective and autonomic regions. Consequently, the ACC as a whole is an excellent candidate for participating in the affective responses to noxious events and the organization of behavioral responses that may be particularly important in maintaining chronic pain. To put that differently, the ACC may be a key site in understanding how A-B-C-D mechanisms integrate and contribute to the chronic pain experience.

Work has begun to provide clues as to how that integration will occur, but much remains open for future work. Exaggerated activity of the ACC in chronic pain patients, for example, might be explained as a consequence of augmented emotional activity during noxious events (99,111). Taken together, however, reviews of the chronic pain and imaging literature generally report reduced activity in the ACC and other regions associated with pain experience (100,109,118). One possibility is that the enhanced pain experience of patients increases the predictability of pain experience and thus reduces the associated neural load (119). Alternatively, chronic pain may simply add noise to the system and reduce the power to detect a response or the ACC may be more active at baseline because of the patient's ongoing pain, making changes due to additional input more difficult to observe (120).

A further possibility, corresponding to that described above in relation to FGID, is that chronic pain has a subcortical rather than a cortical origin and it is interactions between pain and emotion at a subcortical level that determines pain experience. Facilitatory circuits within the brainstem are usually inhibited by cortical input and so the lack of cortical activity may reflect a lack of inhibitory control over noxious information. These speculations require further experimental work.

Another possibility is that one barrier to further progress is the large heterogeneity of chronic pain, which makes it difficult and simply too large for meaningful inferences to be made across patient populations. As has been observed elsewhere (108), the subdivision of chronic pain syndromes into neuropathic, nociceptive, and functional has not clarified mechanistic processes. Similarly, the biopsychosocial model, although a useful heuristic and descriptive tool, does not provide a mechanistic account of pain (109,110). Consequently, the major problems facing chronic pain patients, including status, diagnosis, and treatment, remain unresolved.

Theories require explanations of processes and, at least for now, such explanations are critically absent from the understanding of chronic pain—we still do not know how level B is translated into level A. Brain responses, however, are the final common representation of the processes underlying chronic pain. The application of functional imaging to chronic pain, therefore, provides an opportunity to categorize pain conditions in a more objective manner and provide novel targets for behavioral intervention and analgesic therapy. Functional imaging promises to shed new light onto the complex nature of chronic pain and to potentially redefine these diseases as a series of altered brain states (121).

Placebo

A placebo treatment is one that is expected to have no direct physical or pharmacological benefit—for example, a starch capsule given for anxiety or pain, or a surgery where the critical surgical procedure is not performed. For this reason, placebos are routinely used as comparison conditions in clinical studies, against which to evaluate the effects of investigational treatments. However, placebo treatments have also frequently been used to actually treat a variety of ailments; they have had a place in the healer's repertoire for thousands of years, and are used as clinical treatments by physicians in industrialized countries today with surprising frequency.

Experimental research on placebo effects offers a way to rigorously evaluate the causal effects of expectancies and psychological context (level A) on behavior (level A), brain (level B) and body (level D). The prototypical placebo paradigm involves experimental manipulation of placebo treatment, which permits inferences to be made about its causal effects on the brain and peripheral outcomes (122). It also provides a powerful window into the mechanisms of expectancies and related cognitive processes—mechanisms whose normal function is essential for healthy emotional and cognitive function, and that may interact with pharmacological treatments in patients (123,124). Placebo studies increasingly involve neuroimaging, electrophysiology, and/or peripheral physiological measures to document placebo effects on objective processes and investigate the brain mechanisms by which placebo treatments exert their effects.

To the degree that placebo treatments are healing agents, their power lies in the psycho-biological context surrounding

treatment (125), resulting in an active response in the brain and body of the patient. Whereas many thousands of clinical studies have employed placebo groups as controls against which to evaluate the effects of active medications, very few of these studies contain no-treatment groups against which the psychobiological and clinical effects of the placebo may be evaluated. Thus, improvements in placebo groups are often confounded with sampling bias, natural history effects, regression to the mean, and related statistical artifacts (126,127).

Experimental placebo studies have demonstrated robust effects of placebo on reported pain (123,128–130), and pain is the most well-studied domain in placebo research. Reported pain is a clinically significant measure and the best available measure of pain experience. However, self-reports are limited because they are decision processes that may be influenced by variables that are unrelated to the organic process of nociception and even to actual pain experience (131,132). These issues have prompted a search for more direct physiological measures of various aspects of nociceptive processing and pain experience (133).

Brain imaging studies have now provided evidence on the brain systems involved in both placebo-induced expectancies and changes in pain processing (level B), and on the brain correlates of placebo responses in reported pain (an A-B approach). These studies have involved delivering identical sequences of painful thermal, electrical, or laser stimulation under placebo treatment and a matched control treatment that differed only in the instructions to subjects (134–141). In these studies, placebo and control treatments have been administered within-subjects so that each participant serves as his/her own control. By holding constant the level of the stimulus and randomizing the order of placebo and control treatments, changes in brain activity and reported pain are attributable to the causal effects of the placebo treatment.

One consistent finding in these studies was increases in activity in the pACC and midlateral orbitofrontal cortex (OFC) (136,139,140). These increases seemed to occur during the anticipation of pain (142), when expectancies about an upcoming noxious stimulus are modulated by placebo treatment (136). Changes in the OFC in particular correlated with the magnitude of placebo analgesic responses as reported immediately after painful stimulation. Other studies have provided evidence that placebo treatment elicits the release of endogenous opioids in the pACC and OFC, among other regions. Placebo-induced activation of posterior dorsolateral prefrontal cortex (DLPFC) (136) and dorsal anterior insula (137) have also been reported in anticipation (DLPFC only) and experience of pain, paralleling findings of increased DLPFC activity in placebo responders in other areas such as depression (143,144). As we discuss below, these findings are beginning to outline a system of brain structures that together provide a neuroanatomical basis for the psychological process of cognitive appraisal, which is critical for the generation of emotion-related physiological responses and the appraisal-related modulation of pain and related clinically relevant phenomena.

If placebo treatment affects the brain representation of pain, then one might expect that pain-related activation related to sensory and emotional pain processing would be reduced. Several studies have now provided evidence that placebo treatment reduces activity in pain-processing centers. Wager et al. (136) found placebo-induced reductions in activity in the aMCC, contralateral anterior and mid-insula, and medial thalamus. Price et al. (135) conducted an fMRI study in patients with IBS, who have been shown to have remarkably large placebo effects in pain reports (145). Identical stimulation under placebo versus control conditions resulted in decreases in the aMCC, mid-insula, and medial thalamus. Decreases in other pain-processing regions that may have been related to habituation were present as well.

It is notable that placebo-induced decreases were consistently found in the two studies in regions most closely related to the emotional experience of pain (146,147). One potential mechanism for these decreases is the activation of opioidergic descending anti-nociceptive systems (148–150), a key coordinator of which is the midbrain periaqueductal gray (PAG) (151). The PAG can exert powerful inhibitory effects on nociceptive processes in the spinal cord and brain (152,153), and coordinates other autonomic responses to threat as well (154); it, in turn, is regulated by inputs from the prefrontal cortex (155), providing a neurophysiological basis for the regulation of brainstem homeostatic systems by complex cognition (i.e., placebo expectancies).

Recent evidence supported the idea that the PAG and thus possibly descending anti-nociceptive systems are activated by placebo treatments. Wager et al. (136) reported placebo-induced increases in the PAG during pain anticipation that were correlated with prefrontal increases. Subsequent studies have demonstrated that placebo treatments induce human mu-opioid release in the PAG (140,142), as well as in the same anatomical structures affected in the fMRI studies—the pACC, thalamus, and insula (140,156). Placebo treatment also seems to increase connectivity between the PAG and aMCC in fMRI (135) and opioid-binding studies (140).

Other studies have examined electrical and magnetic correlates of placebo expectancies (157–163), taking advantage of the greater temporal resolution of these techniques. These studies provide evidence that placebo treatments affect relatively rapid responses to noxious stimuli. Together with findings on placebo-induced changes during anticipation, the evidence to date is consistent with the view that placebo-induced expectancies establish a mental context that shapes how noxious stimuli are processed.

The previous studies concern the link between mental processes and brain activity (an A-B approach), and how they relate to the clinically relevant phenomenon of pain experience. The participation of endogenous opioids and PAG in placebo analgesia suggests that placebo treatments may affect information transfer systems (level C) as well, as the PAG is a major control center for the interface between the brain and the autonomic nervous system and the endocrine system (through connections with the hypothalamus), and brain opi-

oids are implicated in immune modulation (160). In addition, the insula and other limbic areas seem to be key mediators of conditioned immunosuppression responses, a profound type of placebo response (161). Studies of placebo-induced changes in autonomic and endocrine activity have demonstrated changes in several peripheral information transfer systems (level C), although much more work needs to be done to understand placebo effects on peripheral physiology (124,164–170). Some recent evidence suggested that placebo analgesia is accompanied by reductions in heart rate and low-frequency (largely sympathetic) heart rate variability, and there have been reports of placebo affects on heart rate (171), blood pressure (171), skin conductance responses (124,164), respiration (165), and—with increased threat related to "nocebo" (expectation of negative outcome) treatments (166,167) or conditioning to an active drug (168)—cortisol. Other conditioning studies have shown changes in biochemical and immune activity (161,169). A recent meta-analysis (170) supported the general view that information transfer systems are more susceptible to placebo effects than are peripheral biochemical processes.

To synthesize the current state of the field, an emerging model is that the largest effects of placebo are found in brain regions at the interface between emotional and cognitive contextual processes (linking levels A and B). When stronger placebo manipulations are available, including the use of conditioning, effects in deeper brainstem structures are more likely that will be associated with changes in autonomic and endocrine activity (an A-B-C approach).

The brain regions most consistently implicated in placebo analgesia, which include the midlateral orbitofrontal cortex (OFC), aMCC, medial thalamus, and anterior insula, are part of a broader network of structures thought to be a neuroanatomical substrate for the computation of abstract reward/punishment value—or, in other terms, appraisal of the significance of a stimulus or context for the well-being and survival of the organism (172). Note the similarity of this conceptualization to the definition of emotion provided in the companion manuscript (1). This extended "appraisal network" includes the medial prefrontal cortex (MPFC), OFC, extended amygdala, nucleus accumbens, ventral striatum, medial thalamus, and the medial temporal lobes. The MPFC network, in particular, projects massively to the PAG and hypothalamus, providing higher cortical control over these intermediate-level regulators of homeostatic responses. All of these regions have shown fMRI and opioid-binding changes during placebo analgesia.

The pattern of neural changes in placebo studies thus suggests that, when placebo manipulations are strong enough, changes in the central appraisal network may be strong enough to influence the PAG and hypothalamic function, and associated spinal anti-nociceptive or other peripheral processes. Thus, expectancy effects are not limited to the cortical mantle and cognitive decision processes; they may also modulate the basic often unconscious processes that maintain physiological homeostasis (172,173). Along these lines, two current frontiers of research are the study of the effects of placebo on the relation between "evaluative" brain systems and peripheral physiology, and the relation between placebo analgesia and threat/safety appraisals in other paradigms.

The prominence of placebo responses in central systems for appraisal of emotional significance establishes a link between placebo analgesia and manipulations of threat and safety appraisals in other paradigms, including threats to social status and physical safety. This link is supported by findings that placebo treatments in other domains, such as negative emotional responding (174) and depression (143,144), modulate similar structures, including the aMCC, OFC, and DLPFC. In addition, appetitive motivational shifts (involving dopamine) in the ventral striatum/nucleus accumbens have been proposed as a common mechanism for placebo effects across disorders (175), and recent studies have found that placebo analgesia is predicted by fMRI responses to anticipated monetary reward (176) and dopamine activity (172) in the nucleus accumbens. It is perhaps no accident that placebo effects have been found in clinical signs and brain activity associated with Parkinson's disease (177), and with increased striatal dopamine activity in patients with Parkinson's disease (178). Such changes may affect the same neurochemical systems underlying motivation and valuation as placebo treatments for pain. Overall, these results are promising, and more study is needed to establish the role of central appraisal systems in placebo responses across different conditions.

DISCUSSION

It should be clear from the foregoing reviews on brain imaging research in relation to cardiovascular regulation, FGID, acute and chronic somatic pain and placebo that we have entered a new era of psychosomatic research in which the neural instantiation of relevant mental processes and their regulatory influence on brainstem and peripheral physiological mechanisms can now be quantified. We have shown that the brain is likely to mediate psychophysiological activation, and relations of psychosocial and psychophysiological factors to CVD; that brain-gut interactions are critical to an understanding of FGID and the perception of visceral pain; that somatic pain perception is influenced in major ways by brain activation as well as peripheral processes; and that placebo effects are mediated by neurochemical changes within increasingly well-defined brain networks. These developments raise questions about the implications of brain imaging for how psychosomatic research is conducted, what the implications are for treatment intervention, what the implications are for mainstream medicine, and what the research priorities are in the next 5 to 10 years.

Implications for Psychosomatic Research

In the first paper in this series (1), we outlined a conceptual approach to the relations among different levels of analysis in psychosomatic research: A = mind, behavior; B = brain; C = information transfer systems (autonomic, neuroendocrine, immune); and D = end organ (e.g., heart). As noted previously, for the past half century, the field has largely conducted

research using an A-D, A-C, and A-C-D approach. We believe that the most important implication of this new perspective is that psychosomatic research shift to include an A-B-C-D model. Doing so essentially means creating a new field of investigation that might be called "brain-body medicine," in which the mechanisms by which the intact human brain influences end-organ function and systemic medical disorders are delineated.

An essential ingredient in this undertaking is to enlist the enthusiastic participation of neuroscientists. The starting point must be a phenomenon that is well established in the psychosomatic literature using the A-C-D approach, such as the association between depression and increased mortality among patients with coronary artery disease (CAD) as mediated by increased blood coagulability or alterations in autonomic tone (179). A critical next step is to formulate a specific brain-based hypothesis that would enable an A-B-C-D approach. If granting agencies provide the needed research funds, and testable hypotheses can be formulated, neuroscientists will be attracted to this area of research. However, it will be essential to create interdisciplinary research teams that include psychosomatic researchers as well as neuroscientists to address specific clinical conditions. Psychosomatic researchers will play a vital role in identifying appropriate topics, helping to formulate brain-based hypotheses within a multilevel explanatory chain and then overseeing the research so that the end product is an A-B-C-D integration.

In the companion manuscript (1), we discussed how, broadly speaking, brainstem mechanisms regulate vital bodily functions and that cortical-subcortical interactions modulate the function of these brainstem mechanisms. Our ability to quantify such relations now was illustrated in the brief review of placebo mechanisms. Nevertheless, brainstem mechanisms of visceral regulation are poorly understood despite the fact that a wide range of new neuroscientific tools are now available to study such mechanisms, e.g., ensemble and field potential recordings from multiple neurons. Because brainstem mechanisms are fairly well conserved across the evolutionary timescale (180), a key ingredient of the brain-body agenda will be to conduct studies in rodents and other animals examining brainstem regulation of cardiovascular, pulmonary, renal, hematopoietic, and musculoskeletal function, in addition to autonomic, endocrine, and immune function. The translation to human conditions will be facilitated by parallel study designs in humans and animals in which cortical-subcortical interactions can be studied with functional brain imaging. Much can be accomplished using currently available functional brain imaging techniques, such as fMRI and PET (with ^{15}O-water) which are based on cerebral blood flow as an indicator of local neuronal activity. As new imaging techniques emerge that enable direct measures of neural activity (e.g. ion flux) with far greater spatial and temporal precision than current methods (181), the correspondence between human and animal studies will be that much greater.

A standard approach in psychosomatic medicine research is to identify stable markers that predict outcomes. For example, high hostility at baseline predicts future development of CAD (A predicts D) (182). This "stable marker" approach can and has been used in functional brain imaging research; e.g., the observation by Gianaros and colleagues that elevated activity in the PCC predicted greater blood pressure reactivity to stress (B predicts C) (20). The A-B-C-D approach, however, also lends itself to a more process-oriented, contextual, systems-oriented approach in which variables at different levels are interacting bidirectionally as in A$\longleftrightarrow$B$\longleftrightarrow$C$\longleftrightarrow$D. A complete A-B-C-D account of any given finding in psychosomatic medicine will ultimately require a complex process-oriented explanation of this type. Only when such a causal chain is delineated will we understand how the association between A and D is accomplished.

Bringing the brain back into psychosomatic medicine may help to advance the D-A paradigm by elucidating brain mechanisms likely to explain the impact of disease on behavior. It may also advance the more traditional A-D and A-C-D risk-oriented approach. In disease contexts such as CAD, a wide variety of negative emotion variables have been linked to adverse cardiac outcomes, including depression, anxiety, hostility, worry, anger, and grief (183). Large-scale studies typically include only one of these variables and none has included all. Doing so would permit determination of the extent to which the variance in clinical outcome is unique or commonly shared. To the extent that the latter predominates, it could lead to a search for the common neural mechanism that could explain such overlap. Once this was identified, it would then be possible to determine the psychological characteristics that correspond to the neural mechanism in question, which might be different from the emotional states listed above. New psychometric measures with potentially more explanatory power could then be developed that could be used clinically as well as in epidemiological studies.

Psychosomatic medicine research is increasingly focused on clinical relevance and using risk data to inform the design of clinical trials. A good example is a clinical trial to treat depression and determine whether this affects cardiovascular outcome. Another key way in which the neuroscience agenda can be advanced is to include measures of brain structure and function in at least a subset of patients in behaviorally-oriented clinical trials. By introducing the brain into an existing A-C-D framework, the potential for rapid advances would be considerable.

Implications for Clinical Intervention

The history of science can be broadly divided into two main approaches: realism, which seeks to describe the world as it really is and how it works, and instrumentalism, a more goal-oriented approach that seeks to make predictions and change the world (184). The foregoing discussion focused on the former approach associated with seeking to understand the A-B-C-D mechanisms by which psychological and social factors influence physical health. At this point, we now consider how this information can potentially be used to improve clinical care and health outcomes.

Depression is associated with increased mortality in heart disease (185), diabetes (186), certain forms of cancer (187), and stroke (188). Antidepressant treatment in stroke patients improves longevity independent of depression status (188). Although clinical trials have not yet been conducted in heart disease, diabetes, and cancer to demonstrate that reversing depression improves longevity, it is nevertheless clinically important to treat depression, and to do so as efficiently and expeditiously as possible. One of the clinical realities of treating depressed patients with antidepressant medications is that we do not yet know how to predict who will respond to which medication. Finding the right medication can be time consuming, as clinical response typically takes at least 4 to 6 weeks. It is noteworthy, therefore, that recent research has shown that pretreatment changes in brain function during a response inhibition task as measured by fMRI predict response to s-citalopram 10 weeks later (189). This line of research may eventually make it possible to predict in advance which medication a patient will respond to, saving valuable time and reducing morbidity.

Practitioners of psychosomatic medicine have always recommended that the unique biological, psychological, and social characteristics of each individual patient be taken into account in clinical care. A new field called "personalized medicine" has emerged with an initial focus on using genetic profiling to predict who will respond to a given medication (190). It is becoming clear that genetics alone will be insufficient and that psychometric, psychophysiologic, and neuroimaging data will all be useful in identifying in advance who is likely to respond to a given treatment (191). The point here is that brain structure and function may play a vital role in the data matrix used for clinical decision-making. Such information could potentially be used together, for example, to determine whether lifestyle changes, relaxation training, social skills training, cognitive-behavioral therapy, other forms of psychotherapy, or any given medication would be the treatment of choice for a given patient with depressive symptoms (192).

As the neural circuitry for specific clinical conditions gets refined, direct stimulation of the brain at strategic locations becomes feasible. Deep brain stimulation (DBS) of the subthalamic nucleus has become an important component of the treatment armamentarium for Parkinson's disease (193). A landmark advance in psychiatry occurred in 2005 when it was demonstrated that DBS of the sACC was an effective treatment for depression in two thirds of treatment refractory patients who had been unresponsive to all other treatments (194). The decision to stimulate this brain structure was based on a network analysis of functional changes in the brain in depression and a determination of which loci were most important. Clinical trials of DBS for obsessive-compulsive disorder involving electrical stimulation of the internal capsule (connecting the thalamus to the frontal lobe) are currently under way (195). As the ways in which the brain contributes to medical conditions are elucidated, and the technology continues to improve and become cheaper, DBS treatment in "psychosomatic" contexts will become feasible in the future.

Rapid transcranial magnetic stimulation (TMS) of the left DLPFC is an effective treatment for depression (196). Although less well studied and probably less effective for depression, slow TMS (sTMS) of the right DLPFC may also have utility in some contexts. For example, in a study of four women with fibromyalgia, depression, and borderline personality disorder, right-sided sTMS decreased pain in all four women and brought about complete resolution of pain in two (only one in four had an antidepressant response) (197).

Vagus nerve stimulation (VNS) has received Food and Drug Administration approval for the treatment of epilepsy and more recently the treatment of depression (198). VNS has not yet been used to treat psychosomatic conditions. Given the importance of the vagus in the cardiovascular, pulmonary, gastrointestinal, and immune systems, and evidence that VNS induces changes in brainstem and limbic structures (199), it is likely only a matter of time before applications of VNS in psychosomatic contexts are identified.

The discussion up to this point has focused on approaches that have already been implemented. Gazing into the crystal ball regarding potential applications in the future, chronic pain is a clinical disorder that often baffles clinicians. In this context, there is often a discrepancy between the objective evidence of tissue damage or abnormality and the degree of subjective pain complaints. It is customary in acute pain contexts to treat the pain sufficiently to provide relief, but chronic use of opiate medications is undesirable, and clinicians have difficulty sorting out the extent to which emotional factors amplify the pain, whether distress is cause, effect, or both, and how best to treat the patient. This is where our emerging understanding of pain circuitry, emotion circuitry, and their interaction in the brain can potentially be useful. It is possible, for example, that functional brain imaging could, in the future, help to sort out and diagnose the relative contributions of each to the pain experience and the response of each to targeted treatments. Related considerations would apply to somatoform disorders as well.

Implications for General Medicine

It is an unfortunate reality that the biomedical model predominates in medicine today and that the biopsychosocial model, which recently celebrated its 40th birthday (200), is still viewed with skepticism. Physician time with patients is limited and third-party payers do not recognize the health and financial benefits of a more integrated approach. This is bewildering to many of us as the advantages of a more comprehensive approach seem obvious.

Under such circumstances, what we fail to recognize is that we have not proven the effectiveness of this comprehensive biopsychosocial approach within the framework of the biomedical model. The A-D and the A-C-D approaches leave gaps that do not allow for a complete mechanistic explanation for how A influences D. Incorporating measurements at level B fills a critical gap that can begin to explain where (if not how) the transformation from mind to body and body to mind occurs. Brain imaging methods alone cannot establish causal-

ity (201), however, because they typically involve correlating one thing (e.g., a mental process) with another (e.g., brain activity). Rather, the ability to make claims about causality is a function of experimental design. Moreover, the meaning of brain imaging findings is typically derived from evidence from a variety of neuroscientific sources, including brain imaging studies in other contexts that implicate a given structure, findings from human lesion studies, and neural tract tracing studies in monkeys. Utilization of appropriate experimental designs, combinations of techniques and special populations are needed to address the direction and timing of interactions across the four levels. In addition, a fully mechanistic account will also ultimately require that neural mechanisms and their influence on pathophysiology are understood at the molecular as well as the molar level. We believe that explicating the A-B-C-D model in this way will begin to address this deficiency and will also introduce new ways to diagnose, treat, and evaluate treatment. The benefits of such an approach would then need to be demonstrated in clinical trials. Once this occurs, the substantial possibility exists that this will alter how medicine is practiced and reimbursed.

As major changes in the healthcare system are now being contemplated by policymakers, there is no time to lose in getting started on this agenda. High priorities for research are to demonstrate "proof of principle" by delineating the A-B-C-D model in at least one medical condition in the next 5 to 10 years. There are many candidate psychosomatic relations that are ripe for this type of investigation, but probably none more promising than those showing how depression influences morbidity and mortality in CVD, diabetes, cancer, or stroke. If it can also be shown that this approach can improve health and save money, a new era of a more humanistic medicine will be initiated. Perhaps the ultimate measure of success would be that the interdisciplinary field of psychosomatic medicine would cease to exist because this approach would become the predominant model in medicine.

CONCLUSION

The field of psychosomatic medicine was founded on the premise that the mind and body were indivisible and interrelated in their influence. This premise was derived, in part, from evidence early in the 20th century that the brain (level B) played a critical role in this integration. It is therefore ironic that, in the past half century, the field of psychosomatic medicine has addressed this integration by studying mind (level A) and body (levels C and D) as separate entities. In the minds of skeptics, such as many of our colleagues in general medicine, this unfortunately may have inadvertently perpetuated the very mind-body dualism that the field was designed to overcome.

In these companion papers, we have sought to highlight the following points:

- A variety of structural and functional brain imaging techniques are now available that permit meaningful study of the brain in psychosomatic medicine research;
- Communication between the brain (level B) and bodily end organs (level D) is accomplished through information transfer systems (level C: autonomic, endocrine, immune);
- Research in psychosomatic medicine should shift to include an A-B-C-D model;
- By demonstrating the mechanisms of an A-B-C-D mind-brain-body causal chain, the boundaries between psychosomatic medicine and general medicine are likely to dissipate.

It is our view, therefore, that the field is at a critical juncture now in which the brain can be reintroduced and studied intensively in relation to the body to produce a paradigm shift in the field of psychosomatic medicine. Achieving this integration through research will have profound implications, not only for how medicine is practiced and how mental and physical health is improved, but perhaps more generally on how we as human beings view ourselves.

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