

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

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Issue:

Volume 71(2), February/March 2009, pp 135-151

Publication Type:

[Review Articles]

Publisher:

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DOI:

10.1097/PSY.0b013e318198a11f

ISSN: 0033-3174

Accession: 00006842-200902000-00002

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Received for publication April 16, 2008; revision received August 27, 2008.

Keywords: neuroscience, anterior cingulate cortex, emotion, pain, cardiovascular regulation, placebo

Abstract

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.

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** = periaqueductal 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.

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 psychosomatic 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).

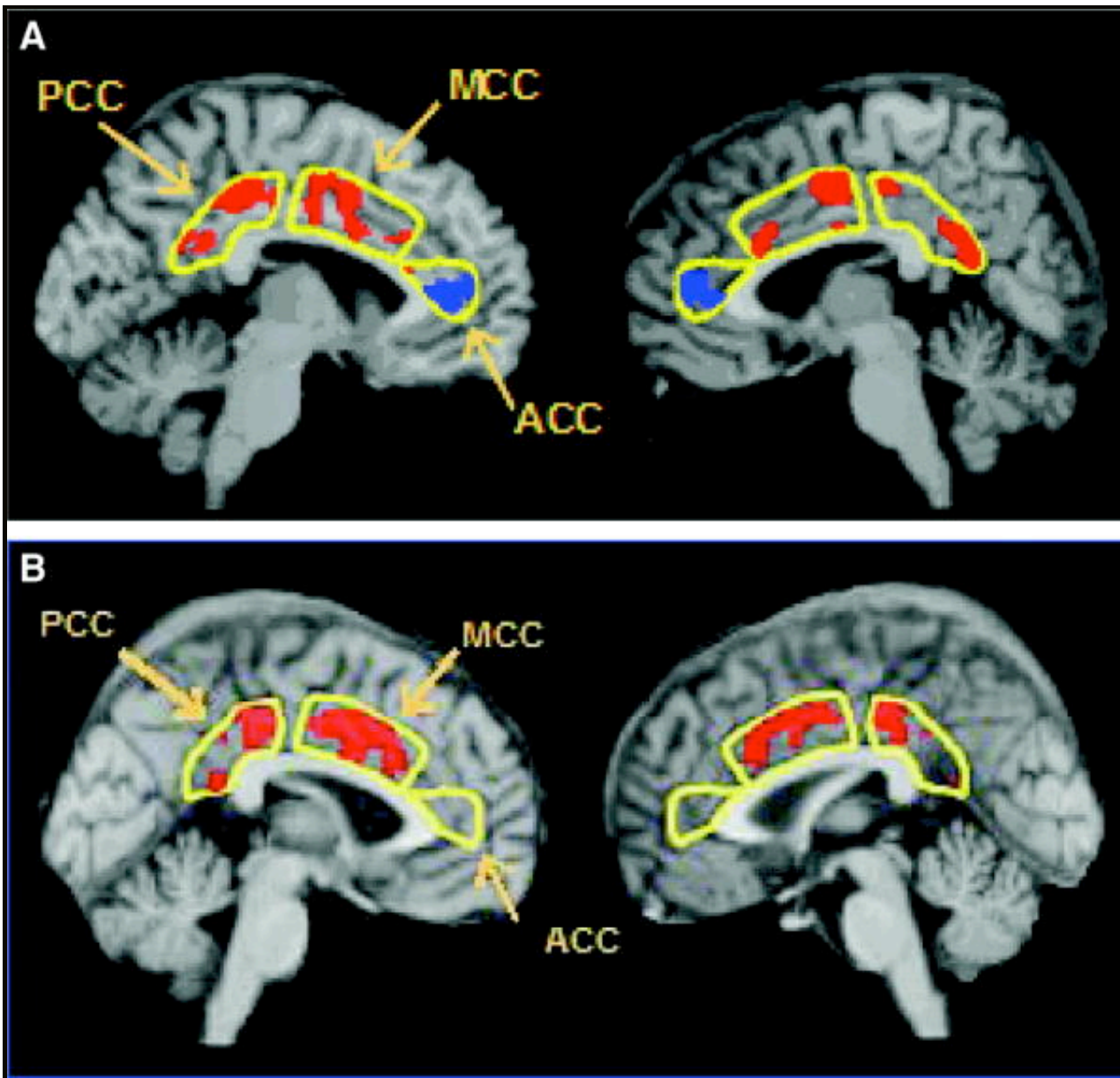


Figure 1. A. Response to painful (50 mm Hg) distensions grouped for patients with a history of IBS and abuse compared with a combined group of patients with only IBS, only abuse history and controls. Greater activation (depicted in red) is seen for the IBS and abuse group compared with the others in 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 distention 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).

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 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, neuroendocrine 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.

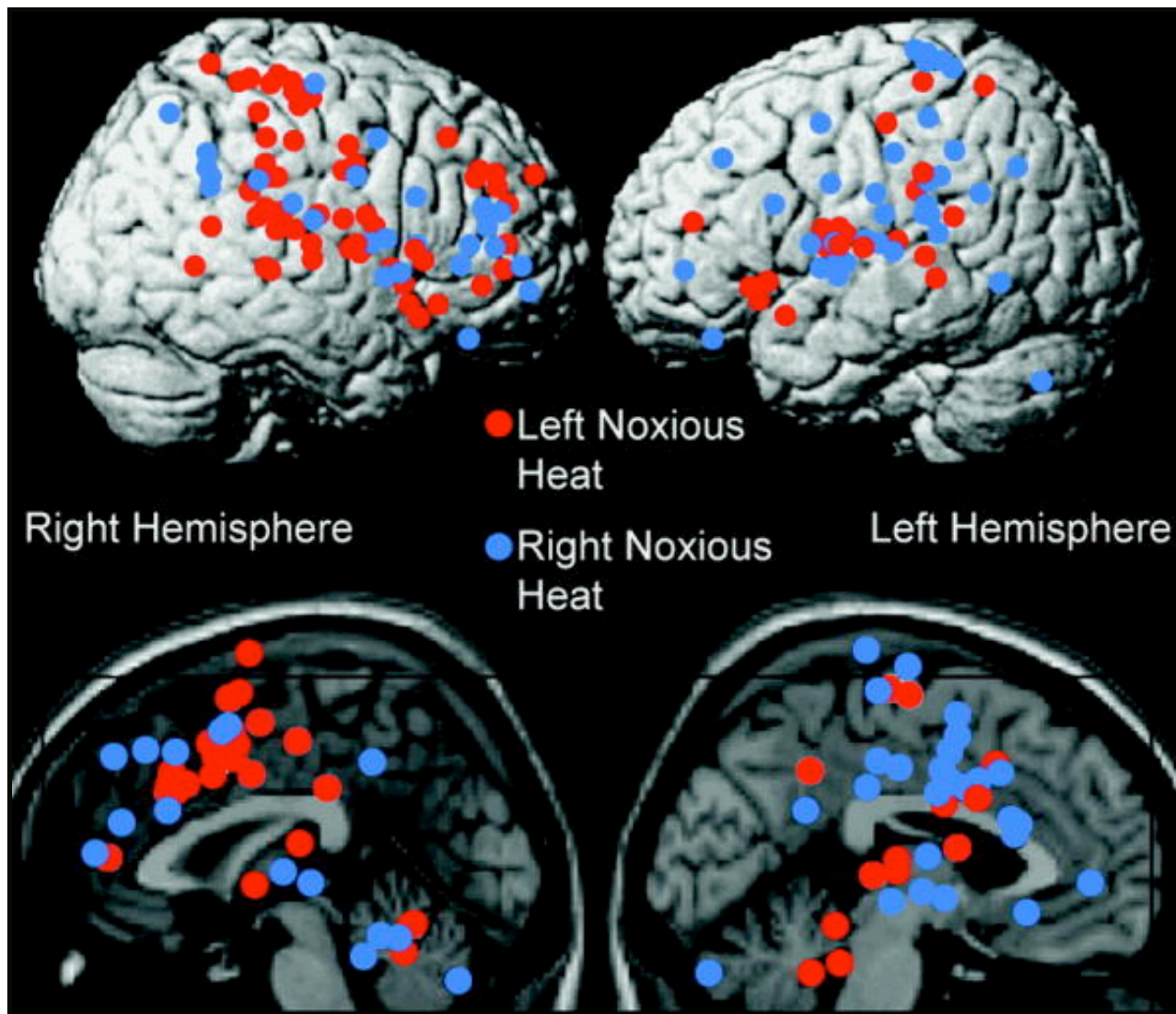


Figure 2. Lateral (top) and medial (bottom) surface activation during painful experience induced with noxious

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).

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 opportunity 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 opioids 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 ¹⁵O-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 \leftrightarrow B \leftrightarrow C \leftrightarrow 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, psychophysiological, 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 causality (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.

REFERENCES

1. Lane RD, Waldstein SR, Chesney MA, Jennings JR, Lovallo WR, Kozel PJ, Rose RM, Drossman DA, Schneiderman N, Thayer JF, Cameron OG. The rebirth of neuroscience in psychosomatic medicine, part I: historical context, methods and relevant basic science. *Psychosom Med* 2009;71:117-34. [\[Context Link\]](#)
2. Gazzaniga MS, Ivry RB, Mangun GR. *Cognitive Neuroscience*. 3rd ed. New York: Norton; 2008. [\[Context Link\]](#)
3. Lane R, Nadel L, Ahern G, Allen J, Kaszniak A, Rapcsak S, Schwartz G, editors. *Cognitive Neuroscience of Emotion*. New York: Oxford University Press; 2000. [\[Context Link\]](#)
4. Cacioppo JT, Visser PS, Pickett CL. *Social Neuroscience: People Thinking About Thinking People*. Cambridge, MA: MIT Press; 2006. [\[Context Link\]](#)
5. Charney DS, Nestler EJ. *Neurobiology of Mental Illness*. 2nd ed. New York: Oxford University Press; 2004. [\[Context Link\]](#)
6. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennery DN, Hoppel BE, Cohen MS, Turner R, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci U S A* 1992;89:5675-9. [\[Context Link\]](#)
7. Illes J, Kirschen MP, Gabrielli JDE. From neuroimaging to neuroethics. *Nat Neurosci* 2003;6:204-5. [\[Context Link\]](#)
8. Dunbar H. *Emotions and Bodily Changes—A Survey of Literature on Psychosomatic Interrelationships 1910-1933*. New York: Columbia University Press; 1935. [\[Context Link\]](#)
9. Zautra AJ. *Emotions, Stress and Health*. New York: Oxford University Press; 2003. [\[Context Link\]](#)
10. Lane R. Neural substrates of implicit and explicit emotional processes: a unifying framework for psychosomatic medicine. *Psychosom Med* 2008;70:213-30. [\[Context Link\]](#)
11. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and

stroke statistics—2006 update. *Circulation* 2006;113:e85-e151. [\[Context Link\]](#)

12. Allender S, Scarborough P, Peto V, Rayner M, Leal J, Luengo-Fernandez R, Gray A. *European Cardiovascular Disease statistics*. 3rd ed. Brussels: European Heart Network; 2008. [\[Context Link\]](#)

13. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;11:e442. [\[Context Link\]](#)

14. Strike PC, Steptoe A. Psychosocial factors in the development of coronary artery disease. *Prog Cardiovasc Dis* 2004;4:337-47. [\[Context Link\]](#)

15. King AB, Menon RS, Hachinski V, Cechetti DF. Human forebrain activation by visceral stimuli. *J Comp Neurol* 1999;413:572-82. [\[Context Link\]](#)

16. Harper RM, Bandler R, Spriggs D, Alger JR. Lateralized and widespread brain activation during transient blood pressure elevation revealed by magnetic resonance imaging. *J Comp Neurol* 2000;417:195-204. [\[Context Link\]](#)

17. Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation. *J Physiol Lond* 2000;523:259-70. [\[Context Link\]](#)

18. Critchley HD, Mathias CJ, Dolan RJ. Neural correlates of first and second-order representation of bodily states. *Nat Neurosci* 2001;4:207-12. [\[Context Link\]](#)

19. Gianaros PJ, Derbyshire SW, May JC, Siegle GJ, Gamalo MA, Jennings JR. Anterior cingulate activity correlates with blood pressure during stress. *Psychophysiology* 2005;42:627-35. [\[Context Link\]](#)

20. Gianaros PJ, May JC, Siegle GJ, Jennings JR. Is there a functional neural correlate of individual differences in cardiovascular reactivity? *Psychosom Med* 2005;67:31-9. [\[Context Link\]](#)

21. Critchley HD, Josephs O, O'Doherty J, Zanini S, Dewar B-K, Mathias CJ, Cipolotti L, Shallice T Dolan RJ. Human cingulate cortex and autonomic cardiovascular control: converging neuroimaging and clinical evidence. *Brain* 2003;126:2139-56. [\[Context Link\]](#)

22. Williams LM, Phillips ML, Brammer MJ, Skerrett D, Lagopoulos J, Rennie C, Bahramali H, Olivieri G, David AS, Peduto A, Gordon E. Arousal dissociates amygdala and hippocampal fear responses: evidence from simultaneous fMRI and skin conductance recording. *Neuroimage* 2001;14:1070-9. [\[Context Link\]](#)

23. Jennings JR. Autoregulation of blood pressure and thought: preliminary results of an application of brain imaging to psychosomatic medicine. *Psychosom Med* 2003;65:384-95. [\[Context Link\]](#)

24. Gianaros PJ, Van Der Veen FM, Jennings JR. Regional cerebral blood flow correlates with heart period and high-frequency heart period variability during working-memory tasks: implications for the cortical and subcortical regulation of cardiac autonomic activity. *Psychophysiology* 2004;41:521-30. [\[Context Link\]](#)

25. Dalton KM, Kalin NH, Grist TM, Davidson RJ. Neural-cardiac coupling in threat-evoked anxiety. *J Cogn Neurosci* 2005;17:969-80. [\[Context Link\]](#)
26. Ringel Y, Drossman DA, Leserman JL, Suyenobu BY, Wilber K, Lin W, Whitehead WE, Naliboff BD, Berman S, Mayer EA. Effect of abuse history on pain reports and brain responses to aversive visceral stimulation: an fMRI study. *Gastroenterology* 2008;134:396-404. [\[Context Link\]](#)
27. Lane RD, Reiman EM, Ahern GL, Thayer JF. Activity in the medial prefrontal cortex correlates with vagal component of heart rate variability. *Brain Cogn* 2001;47:97-100. [\[Context Link\]](#)
28. Matthews SC, Paulus MP, Simmons AN, Nelesen RA, Dimsdale JE. Functional subdivisions within anterior cingulate cortex and their relationship to autonomic nervous system function. *Neuroimage* 2004;22:1151-56. [\[Context Link\]](#)
29. Treiber FA, Kamarck T, Schneiderman N, Sheffield D, Kapuku G, Taylor T. Cardiovascular reactivity and development of preclinical and clinical disease states. *Psychosom Med* 2003;65:46-62. [\[Context Link\]](#)
30. Jennings JR, Kamarck TW, Everson-Rose SA, Kaplan GA, Manuck SB, Salonen JT. Exaggerated blood pressure responses during mental stress are prospectively related to enhanced carotid atherosclerosis in middle-aged Finnish men. *Circulation* 2004;110:2198-203. [\[Context Link\]](#)
31. Matthews KA, Zhu S, Tucker DC, Whooley MA. Blood pressure reactivity to psychological stress and coronary calcification in the coronary artery risk development in young adults study. *Hypertension* 2006;47:391-5. [\[Context Link\]](#)
32. Soufer R, Bremner JD, Arrighi JA, Cohen I, Zaret BL, Burg MM, Goldman-Rakic P. Cerebral cortical hyperactivation in response to mental stress in patients with coronary artery disease. *Proc Natl Acad Sci U S A* 1998;95:6454-9. [\[Context Link\]](#)
33. Lown B. Sudden cardiac death: biobehavioral perspective. *Circulation* 1987;76:1186-1196. [\[Context Link\]](#)
34. Carroll D, Smith GD, Shipley MJ, Steptoe A, Brunner EJ, Marmot MG. Blood pressure reactions to acute psychological stress and future blood pressure status: a 10-year follow-up of men in the Whitehall II study. *Psychosom Med* 2001;63:737-43. [\[Context Link\]](#)
35. Thayer JF, Lane RD. The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psychol* 2007;74:224-42. [\[Context Link\]](#)
36. O'Connor MF, Gündel H, McRae K, Lane RD. Baseline vagal tone predicts BOLD response during elicitation of grief. *Neuropsychopharmacology* 2007;32:2184-9. [\[Context Link\]](#)
37. Gianaros PJ, Horenstein JA, Cohen S, Matthews KA, Brown SM, Flory JD, Critchley HD, Manuck SB, Hariri AR. Perigenual anterior cingulate morphology covaries with perceived social standing. *Soc Cogn Affect Neurosci* 2007;2:161-73. [\[Context Link\]](#)

38. Gianaros PJ, Jennings JR, Sheu LK, Greer PJ, Kuller LH, Matthews KA. Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. *Neuroimage* 2007;35:795-803. [\[Context Link\]](#)
39. Verrier R, Calvert A, Lown B. Effect of posterior hypothalamic stimulation on ventricular fibrillation threshold. *Am J Physiol* 1975;228:923-7. [\[Context Link\]](#)
40. Oppenheimer SM, Cechetto DF, Hachinski VC. Cerebrogenic cardiac arrhythmias. Cerebral electrocardiographic influences and their role in sudden death. *Arch Neurol* 1990;47:513-9. [\[Context Link\]](#)
41. Fries R, Konig J, Schafers HJ, Bohm M. Triggering effect of physical and mental stress on spontaneous ventricular tachyarrhythmias in patients with implantable cardioverter-defibrillators. *Clin Cardiol* 2002;25:474-8. [\[Context Link\]](#)
42. Lane RD, Schwartz GE. Induction of lateralized sympathetic input to the heart by the CNS during emotional arousal: a possible neurophysiologic trigger of sudden cardiac death. *Psychosom Med* 1987;49:274-84. [\[Context Link\]](#)
43. Taggart P, Sutton P, Redfern C, Batchvarov VN, Hnatkova K, Malik M, James U, Joseph A. The effect of mental stress on the non-dipolar components of the T wave: modulation by hypnosis. *Psychosom Med* 2005;67:376-83. [\[Context Link\]](#)
44. Critchley HD, Taggart P, Sutton PM, Holdright DR, Batchvarov V, Hnatkova K, Malik M, Dolan RJ. Mental stress and sudden cardiac death: asymmetric midbrain activity as a linking mechanism. *Brain* 2005;128:75-85. [\[Context Link\]](#)
45. Gray MA, Taggart P, Sutton PM, Groves D, Holdright DR, Bradbury D, Brull D, Critchley HD. A cortical potential reflecting cardiac function. *Proc Natl Acad Sci U S A* 2007;104:6818-23. [\[Context Link\]](#)
46. Rosen SD, Paulesu E, Nihoyannopoulos P, Tousoulis D, Frackowiak RS, Frith CD, Jones T, Camici PG. Silent ischemia as a central problem: regional brain activation compared in silent and painful myocardial ischemia. *Ann Intern Med* 1996;124:939-49. [\[Context Link\]](#)
47. Rosen SD, Paulesu E, Wise RJ, Camici PG. Central neural contribution to the perception of chest pain in cardiac syndrome X. *Heart* 2002;87:513-9. [\[Context Link\]](#)
48. Wiens S, Mezzacappa ES, Katkin ES. Heartbeat detection and the experience of emotions. *Cogn Emot* 2000;14:417-27. [\[Context Link\]](#)
49. Critchley HD, Wiens S, Rotshtein P, Ohman A, Dolan RJ. Neural systems supporting interoceptive awareness. *Nat Neurosci* 2004;7:189-95. [\[Context Link\]](#)
50. Pollatos O, Schandry R, Auer DP, Kaufmann C. Brain structures mediating cardiovascular arousal and interoceptive awareness. *Brain Res* 2007;1141:178-87. [\[Context Link\]](#)

51. Gray MA, Harrison NA, Wiens S, Critchley HD. Modulation of emotional appraisal by false physiological feedback during fMRI. *PLoS ONE* 2007;2:e546. [\[Context Link\]](#)
52. Waldstein SR, Elias MF. *Neuropsychology of Cardiovascular Disease*. Mahwah, NJ: Lawrence Erlbaum Associates; 2001. [\[Context Link\]](#)
53. Waldstein, SR, Tankard CF, Maier KJ, Pelletier JR, Snow J, Gardner AW, Macko R, Katzel LI. Peripheral arterial disease and cognitive function. *Psychosom Med* 2003;65:757-63. [\[Context Link\]](#)
54. Jennings JR, Muldoon MF, Ryan C, Price JC, Greer P, Sutton-Tyrrell K, van der Veen FM, Meltzer CC. Reduced cerebral blood flow response and compensation among patients with untreated hypertension. *Neurology* 2005;64:1358-65. [\[Context Link\]](#)
55. Waldstein SR, Katzel, LI. Stress-induced blood pressure reactivity and cognitive function. *Neurology* 2005;64:1750-5. [\[Context Link\]](#)
56. Waldstein SR, Siegel EL, Lefkowitz D, Maier KJ, Pelletier Brown JR, Obuchowski AM, Katzel LI. Stress-induced blood pressure reactivity and silent cerebrovascular disease. *Stroke* 2004;35:1294-8. [\[Context Link\]](#)
57. Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen J. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. *Stroke* 2001;32:1263-70. [\[Context Link\]](#)
58. Kamarck TW, Everson SA, Kaplan GA, Manuck SB, Jennings JR, Salonen JT. Exaggerated blood pressure responses during mental stress are associated with enhanced carotid atherosclerosis in middle-aged Finnish men. Findings from the Kuopio ischemic heart disease study. *Circulation* 1997;96:3842-8. [\[Context Link\]](#)
59. Ouyang A, Locke GR. Overview of neurogastroenterology-gastrointestinal motility and functional GI disorders: classification, prevalence, and epidemiology. *Gastroenterology Clin North Am* 2007;36:485-98. [\[Context Link\]](#)
60. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006;130:1377-90. [\[Context Link\]](#)
61. Hobson AR, Aziz Q. Brain imaging and functional gastrointestinal disorders: has it helped our understanding? *Gut* 2004;53:1198-206. [\[Context Link\]](#)
62. Drossman DA. Brain imaging and its implications for studying centrally targeted treatments in IBS: a primer for gastroenterologists. *Gut* 2005;54:569-73. [\[Context Link\]](#)
63. Gwee KA, Leong YL, Graham C, McKendrick MW, Collins SM, Walters SJ, Underwood JE, Read NW. The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999;44:400-6. [\[Context Link\]](#)
64. Dunlop SP, Jenkins D, Neal KR, Spiller RC. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfections IBS. *Gastroenterology* 2003;125:1651-9. [\[Context Link\]](#)

65. Drossman DA. Mind over matter in the postinfective irritable bowel. *Gut* 1999;44:306-7. [\[Context Link\]](#)
66. Sperber AD, Morris CB, Greemberg L, Bangdiwala SI, Goldstein D, Sheiner E, Rusabrov Y, Hu Y, Katz M, Freud T, Neville A, Drossman DA. Development of abdominal pain and IBS following gynecological surgery: a prospective, controlled study. *Gastroenterology* 2008;134:75-84. [\[Context Link\]](#)
67. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002;123:2108-31. [\[Context Link\]](#)
68. Drossman DA, Creed FH, Olden KW, Svedlund J, Toner BB, Whitehead WE. Psychosocial aspects of the functional gastrointestinal disorders. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, editors. *Rome II. The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology and Treatment: A Multinational Consensus*. 2nd ed. McLean, VA: Degnon Associates; 2000. [\[Context Link\]](#)
69. Mayer EA, Naliboff BD, Chang L, Coutinho SV. Stress and the gastrointestinal tract v. stress and irritable bowel syndrome. *Am J Physiol Gastrointest Liver Physiol* 2001;280:G519-G524. [\[Context Link\]](#)
70. Derbyshire SW. Visceral afferent pathways and functional brain imaging. *Scientific World J* 2003;3:1065-80. [\[Context Link\]](#)
71. Hobday DI, Aziz Q, Thacker N, Hollander I, Jackson A, Thompson DG. A study of the cortical processing of ano-rectal sensation using functional MRI. *Brain* 2001;124:361-8. [\[Context Link\]](#)
72. Vogt BA, Hof PR, Vogt LJ. Cingulate gyrus. In: Paxinos G, Mai JK, editors. *The Human Nervous System*. 2nd ed. San Diego: Elsevier Academic Press, 2004. [\[Context Link\]](#)
73. Vogt BA, Berger GR, Derbyshire SW. Structural and functional dichotomy of human midcingulate cortex. *Eur J Neurosci* 2003;18:3134-44. [\[Context Link\]](#)
74. Vogt BA, Watanabe H, Grootenk S, Jones AKP. Topography of diprenorphine binding in human cingulate gyrus and adjacent cortex derived from coregistered PET and MR images. *Hum Brain Mapp* 1995;3:1-12. [\[Context Link\]](#)
75. Petrovic P, Ingvar M. Imaging cognitive modulation of pain processing. *Pain* 2002;95:1-5. [\[Context Link\]](#)
76. Vogt BA, Sikes RW. The medial pain system, cingulate cortex, and parallel processing of nociceptive information. In: Mayer EA and Saper CB, editors. *The Biological Basis for Mind Body Interactions*. 1st ed. Los Angeles: Elsevier Science BV; 2000. [\[Context Link\]](#)
77. Mertz H, Morgan V, Tanner G, Pickens D, Price R, Shyr Y, Kessler R. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology* 2000;118:842-8. [\[Context Link\]](#)
78. Naliboff BD, Derbyshire SWG, Munakata J, Berman S, Mandelkern M, Chang L, Mayer EA. Cerebral activation in irritable bowel syndrome patients and control subjects during rectosigmoid stimulation.

Psychosom Med 2001;63:365-75. [\[Context Link\]](#)

79. Drossman DA, Ringel Y, Vogt B, Leserman J, Lin W, Smith JK, Whitehead W. Alterations of brain activity associated with resolution of emotional distress and pain in a case of severe IBS. *Gastroenterology* 2003;124:754-61. [\[Context Link\]](#)

80. Chang L, Berman S, Mayer EA, Suyenobu B, Derbyshire S, Naliboff B, Vogt B, FitzGerald L, Mandelkern MA. Brain responses to visceral and somatic stimuli in patients with irritable bowel syndrome with and without fibromyalgia. *Am J Gastroenterology* 2003;98:1354-61. [\[Context Link\]](#)

81. Verne GN, Himes NC, Robinson ME, Gopinath KS, Briggs RW, Crosson B, Price DD. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. *Pain* 2003;103:99-110. [\[Context Link\]](#)

82. Ringel Y, Drossman DA, Leserman J, Lin W, Liu H, Smith JK, An H, Vogt B, Whitehead WE. IBS diagnosis and a history of abuse have synergistic effect on the perigenual cingulate activation in response to rectal distention. *Gastroenterology* 2003;124:A531. [\[Context Link\]](#)

83. Ringel Y, Drossman DA, Turkington TG, Hawk TC, Bradshaw B, Coleman RE, Whitehead WE. Regional brain activation in response to rectal distention in patients with irritable bowel syndrome and the effect of a history of abuse. *Dig Dis Sci* 2003;48:1774-81. [\[Context Link\]](#)

84. Silverman DHS, Munakata JA, Ennes H, Mandelkern MA, Hoh CK, Mayer EA. Regional cerebral activity in normal and pathologic perception of visceral pain. *Gastroenterology* 1997;112:64-72. [\[Context Link\]](#)

85. Taber KH, Rauch SL, Lanius RA, Hurley RA. Functional magnetic resonance imaging: application to posttraumatic stress disorder. *J Neuropsychiatry Clin Neurosci* 2003;15:125-9. [\[Context Link\]](#)

86. Eisenberger NI, Lieberman MD, Williams KD. Does rejection hurt? An fMRI study of social exclusion. *Science* 2003;302:290-2. [\[Context Link\]](#)

87. Bub DN. Methodological issues confronting PET and fMRI studies of cognitive function. *Cogn Neuropsychol* 2000;17:467-84. [\[Context Link\]](#)

88. Phan KL, Wager TD, Taylor SF, Liberzon I. Functional neuroimaging studies of human emotions. *CNS Spectrums* 2004;9:258-66. [\[Context Link\]](#)

89. Morgan V, Pickens D, Shyr Y. Anxiety is associated with increased anterior cingulate but not thalamic activation during rectal pain in IBS and controls. *Gastroenterology* 2001;120(Suppl 1):A714-5, Abstract 3850. [\[Context Link\]](#)

90. Ringel Y, Drossman DA, Leserman J, Lin W, Liu H, Vogt B, Whitehead WE. Association of anterior cingulate cortex (ACC) activation with psychosocial distress and pain reports. *Gastroenterology* 2003;124:A97. [\[Context Link\]](#)

91. Lackner JM, Lockwood A, Coad M, Mahl TC, Firth R, Mertz HR, Katz L, Krasner S, Wack DC, Galantowicz P. Alterations in GI symptoms, psychological status, and brain function following participation in cognitive therapy for IBS. *Gastroenterology* 2004;126:222. [\[Context Link\]](#)
92. Morgan V, Pickens D, Gautam S, Kessler R, Mertz H. Amitriptyline reduces rectal pain-related activation of the anterior cingulate cortex in patients with irritable bowel syndrome. *Gut* 2005;54:601-7. [\[Context Link\]](#)
93. Drossman DA, Li Z, Leserman J, Toomey TC, Hu Y. Health status by gastrointestinal diagnosis and abuse history. *Gastroenterology* 1996;110:999-1007. [\[Context Link\]](#)
94. Paivio SC, Laurent C. Empathy and emotion regulation: reprocessing memories of childhood abuse. *J Clin Psychol* 2001;57:213-26. [\[Context Link\]](#)
95. Talbot JD, Marret S, Evans AC, Meyer E, Bushnell MC, Duncan GH. Multiple representations of pain in human cerebral cortex. *Science* 1991;251:1355-8. [\[Context Link\]](#)
96. Jones APK, Brown WD, Friston KJ, Qi LY, Frackowiak RSJ. Cortical and subcortical localization of response to pain in man using positron emission tomography. *Proc R Soc Lond* 1991;244:39-44. [\[Context Link\]](#)
97. Casey KL, Minoshima S, Berger KL, Koeppe RA, Morrow TJ, Frey KA. Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. *J Neurophysiol* 1994;71:802-7. [\[Context Link\]](#)
98. Coghill RC, Talbot JD, Evans AC, Meyer E, Gjedde A, Bushnell MC, Duncan GH. Distributed processing of pain and vibration by the human brain. *J Neurosci* 1994;14:4095-108. [\[Context Link\]](#)
99. Derbyshire SWG, Jones AKP, Devani P, Friston KJ, Feinmann C, Harris M, Pearce S, Watson JDG, Frackowiak RSJ. Cerebral responses to pain in patients with atypical facial pain measured by positron emission tomography. *J Neurol Neurosurg Psychiatry* 1994;57:1166-73. [\[Context Link\]](#)
100. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 2005;9:463-84. [\[Context Link\]](#)
101. Vogt B. Pain and emotion interactions in subregions of the cingulate cortex. *Nat Rev Neurosci* 2005;6:533-44. [\[Context Link\]](#)
102. Keefe FJ, Dunsmore J, Burnett R. Behavioral and cognitive-behavioral approaches to chronic pain: recent advances and future directions. *J Consult Clin Psychol* 1992;60:528-36. [\[Context Link\]](#)
103. Drossman DA. Gastrointestinal illness and the biopsychosocial model. *J Clin Gastroenterol* 1996;22:252-4. [\[Context Link\]](#)
104. Turk DC, Rudy TE. Cognitive factors and persistent pain: a glimpse into Pandora's box. *Cognit Ther Res* 1992;16:99-122. [\[Context Link\]](#)

105. Harstall C. How prevalent is chronic pain? *Pain: Clinical Updates* 2003;XI:1-4. [\[Context Link\]](#)
106. McFarlane GJ, McBeth J, Silman AJ. Widespread body pain and mortality: prospective population based study. *Br Med J* 2001;323:1-4. [\[Context Link\]](#)
107. Maetzel A, Li L. The economic burden of low back pain: a review of studies published between 1996 and 2001. *Best Pract Res Clinic Rheumatol* 2002;16:23-30. [\[Context Link\]](#)
108. Borsook D, Becerra LR. Breaking down the barriers: fMRI applications in pain, analgesia and analgesics. *Mol Pain* 2006;2:30. [\[Context Link\]](#)
109. Derbyshire SWG. Exploring the pain “neuromatrix.” *Curr Rev Pain* 2000;6:467-7. [\[Context Link\]](#)
110. Derbyshire SWG, Osborn J. Modelling pain circuits: how imaging may modify perception. *Neuroimaging Clin* 2007;17:485-93. [\[Context Link\]](#)
111. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthrit Rheum* 2002;46:1333-43. [\[Context Link\]](#)
112. Giesecke J, Gracely RH, Grant MA, Nachevson A, Petzke F, Williams DA, Clauw DJ. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthrit Rheum* 2004;50:613-22. [\[Context Link\]](#)
113. Gracely RH, Geisser ME, Giesecke T, Grant MA, Petzke F, Williams DA, Clauw DJ. Pain catastrophizing and neural responses to pain among persons with fibromyalgia. *Brain* 2004;127:835-43. [\[Context Link\]](#)
114. Lorenz J, Casey KL. Imaging of acute versus pathological pain in humans. *Eur J Pain* 2005;9:163-5. [\[Context Link\]](#)
115. MacLean PD. Psychosomatic disease and the “visceral brain.” Recent developments bearing on the Papez theory of emotion. *Psychosom Med* 1949;11:338-53. [\[Context Link\]](#)
116. Papez JW. A proposed mechanism of emotion. *Arch Neurol Psychiatry* 1937;28:725-43. [\[Context Link\]](#)
117. Vogt BA, Gabriel M. *Neurobiology of Cingulate Cortex and Limbic Thalamus*. Boston: Birkhauser; 1993. [\[Context Link\]](#)
118. Derbyshire SWG. Meta-analysis of thirty-four independent samples studied using PET reveals a significantly attenuated central response to noxious stimulation in clinical pain patients. *Curr Rev Pain* 1999;3:265-80. [\[Context Link\]](#)
119. Helmchen C, Mohr C, Erdmann C, Binkofski F, Büchel C. Neural activity related to self-versus externally-generated painful stimuli reveals distinct differences in the lateral pain system in a parametric fMRI study. *Hum Brain Mapp* 2006;27:755-65. [\[Context Link\]](#)

120. Derbyshire SWG. Burning questions about the brain in pain. *Pain* 2006;122:217-8. [\[Context Link\]](#)
121. Borsook D, Moulton EA, Schmidt KF, Becerra LR. Neuroimaging revolutionizes approaches to chronic pain. *Mol Pain* 2007;3:25. [\[Context Link\]](#)
122. Rubin DB. Which ifs have causal answers. *J Am Stat Assoc* 1986;81:961-2. [\[Context Link\]](#)
123. Benedetti F, Amanzio M, Maggi G. Potentiation of placebo analgesia by proglumide. *Lancet* 1995;346:1231. [\[Context Link\]](#)
124. Flaten MA, Simonsen T, Olsen H. Drug-related information generates placebo and nocebo responses that modify the drug response. *Psychosom Med* 1999;61:250-5. [\[Context Link\]](#)
125. Moerman DE. Meaning, medicine, and the “placebo effect.” *Cambridge Studies in Medical Anthropology* (No. 9). New York: Cambridge University Press; 2002. [\[Context Link\]](#)
126. Hrobjartsson A, Gotzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2004;3:CD003974. [\[Context Link\]](#)
127. Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? *J Clin Epidemiol* 1997;50:1311-8. [\[Context Link\]](#)
128. Price DD, Milling LS, Kirsch I, Duff A, Montgomery GH, Nicholls SS. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 1999;83:147-56. [\[Context Link\]](#)
129. Voudouris NJ, Peck CL, Coleman G. The role of conditioning and verbal expectancy in the placebo response. *Pain* 1990;43:121-8. [\[Context Link\]](#)
130. Wager TD. The neural bases of placebo effects in pain. *Current Directions in Psychol Sci* 2005;14:175-9. [\[Context Link\]](#)
131. Allan LG, Siegel S. A signal detection theory analysis of the placebo effect. *Evaluation & the Health Professions* 2002;25:410-20. [\[Context Link\]](#)
132. Clark WC. Somatosensory and pain measurement by statistical and sensory decision theory. In: Adelman G, Smith B, editors. *Encyclopedia of Neuroscience*. Amsterdam: Elsevier; 2003. [\[Context Link\]](#)
133. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. *Ann Rev Pharmacol Toxicol* 2008;48:33-60. [\[Context Link\]](#)
134. Bingel U, Lorenz J, Schoell E, Weiller C, Büchel C. Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. *Pain* 2006;120:8-15. [\[Context Link\]](#)
135. Price DD, Craggs J, Verne GN, Perlstein WM, Robinson ME. Placebo analgesia is accompanied by large reductions in pain-related brain activity in irritable bowel syndrome patients. *Pain* 2007;127:63-72. [\[Context Link\]](#)

[Link](#)

136. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 2004;303:1162-7. [\[Context Link\]](#)
137. Kong J, Gollub RL, Rosman IS, Webb JM, Vangel MG, Kirsch I, Kaptchuk TJ. Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging. *J Neurosci* 2006;26:381-8. [\[Context Link\]](#)
138. Lieberman MD, Jarcho JM, Berman S, Naliboff BD, Suyenobu BY, Mandelkern M, Mayer EA. The neural correlates of placebo effects: a disruption account. *Neuroimage* 2004;22:447-55. [\[Context Link\]](#)
139. Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia—imaging a shared neuronal network. *Science* 2002;295:1737-40. [\[Context Link\]](#)
140. Wager TD, Scott DJ, Zubieta JK. Placebo effects on human mu-opioid activity during pain. *Proc Natl Acad Sci U S A* 2007;104:11056-61. [\[Context Link\]](#)
141. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch Gen Psychiatry* 2008;65:220-31. [\[Context Link\]](#)
142. Porro CA, Baraldi P, Pagnoni G, Serafini M, Facchin P, Maieron M, Nichelli P. Does anticipation of pain affect cortical nociceptive systems? *J Neurosci* 2002;22:3206-14. [\[Context Link\]](#)
143. Leuchter AF, Cook IA, Witte EA, Morgan M, Abrams M. Changes in brain function of depressed subjects during treatment with placebo. *Am J Psychiatry* 2002;159:122. [\[Context Link\]](#)
144. Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, Jerabek PA. The functional neuroanatomy of the placebo effect. *Am J Psychiatry* 2002;159:728-37. [\[Context Link\]](#)
145. Vase L, Robinson ME, Verne GN, Price DD. Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain* 2005;115:338-47. [\[Context Link\]](#)
146. Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. *Nat Neurosci* 2000;3:184-90. [\[Context Link\]](#)
147. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997;277:968-71. [\[Context Link\]](#)
148. Benedetti F, Arduino C, Amanzio M. Somatotopic activation of opioid systems by target-directed expectations of analgesia. *J Neurosci* 1999;19:3639-48. [\[Context Link\]](#)
149. Fields HL, Levine JD. Biology of placebo analgesia. *Am J Med* 1981;70:745-6. [\[Context Link\]](#)

150. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971-9. [\[Context Link\]](#)
151. Hosobuchi Y. Subcortical electrical stimulation for control of intractable pain in humans. Report of 122 cases (1970-1984). *J Neurosurg* 1986;64:543-53. [\[Context Link\]](#)
152. Dostrovsky JO, Shah Y, Gray BG. Descending inhibitory influences from periaqueductal gray, nucleus raphe magnus, and adjacent reticular formation. II. Effects on medullary dorsal horn nociceptive and nonnociceptive neurons. *J Neurophysiol* 1983;49:948-60. [\[Context Link\]](#)
153. Yang ZL, Zhang YQ, Wu GC. Effects of microinjection of OFQ into PAG on spinal dorsal horn WDR neurons in rats. *Brain Res* 2001;888:167-71. [\[Context Link\]](#)
154. Behbehani MM. Functional characteristics of the midbrain periaqueductal gray. *Prog Neurobiol* 1995;46:575-605. [\[Context Link\]](#)
155. Zhang YQ, Tang JS, Yuan B, Jia H. Inhibitory effects of electrically evoked activation of ventrolateral orbital cortex on the tail-flick reflex are mediated by periaqueductal gray in rats. *Pain* 1997;72:127-35. [\[Context Link\]](#)
156. Zubieta JK, Bueller JA, Jackson LR, Schott DJ, Xu Y, Koeppe RA, Nichols TE, Stohler CS. Placebo effects mediated by endogenous opioid activity on mu-opioid receptors. *J Neurosci* 2005;25:7754-62. [\[Context Link\]](#)
157. Wager TD, Matre D, Casey KL. Placebo effects in laser-evoked pain potentials. *Brain Behav Immun* 2006;20:219-30. [\[Context Link\]](#)
158. Lorenz J, Hauck M, Paur RC, Nakamura Y, Zimmermann R, Bromm B, Engel AK. Cortical correlates of false expectations during pain intensity judgments—a possible manifestation of placebo/nocebo cognitions. *Brain Behav Immun* 2005;19:283-95. [\[Context Link\]](#)
159. Goffaux P, Redmond WJ, Rainville P, Marchand S. Descending analgesia—when the spine echoes what the brain expects. *Pain* 2007;130:137-43. [\[Context Link\]](#)
160. Taub DD, Eisenstein TK, Geller EB, Adler MW, Rogers TJ. Immunomodulatory activity of mu- and kappa-selective opioid agonists. *Proc Natl Acad Sci U S A* 1991;88:360. [\[Context Link\]](#)
161. Pacheco-Lopez G, Niemi MB, Kou W, Härting M, Fandrey J, Schedlowski M. Neural substrates for behaviorally conditioned immunosuppression in the rat. *J Neurosci* 2005;25:2330-7. [\[Context Link\]](#)
162. Watson A, El-Deredy W, Vogt BA, Jones, AKP. Placebo analgesia is not due to compliance or habituation: EEG and behavioural evidence. *NeuroReport* 2007;18:771. [\[Context Link\]](#)
163. Colloca L, Tinazzi M, Recchia S, Le Pera D, Fiaschi A, Benedetti F, Valeriani M. Learning potentiates neurophysiological and behavioral placebo analgesic responses. *Pain* 2008;139:306-14. [\[Context Link\]](#)
164. Flaten MA, Blumenthal TD. Caffeine-associated stimuli elicit conditioned responses: an experimental

model of the placebo effect. *Psychopharmacology* 1999;145:105-12. [\[Context Link\]](#)

165. Benedetti F, Amanzio M, Baldi S, Casadio C, Maggi G. Inducing placebo respiratory depressant responses in humans via opioid receptors. *Eur J Neurosci* 1999;11:625-31. [\[Context Link\]](#)

166. Johansen O, Brox J, Flaten MA. Placebo and nocebo responses, cortisol, and circulating beta-endorphin. *Psychosom Med* 2003;65:786-90. [\[Context Link\]](#)

167. Benedetti F, Amanzio M, Vighetti S, Asteggiano G. The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J Neurosci* 2006;26:12014-22. [\[Context Link\]](#)

168. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci* 2003;23:4315-23. [\[Context Link\]](#)

169. Ader R, Cohen N. Behaviorally conditioned immunosuppression and murine systemic lupus erythematosus. *Science* 1982;215:1534-6. [\[Context Link\]](#)

170. Meissner K, Distel H, Mitzdorf U. Evidence for placebo effects on physical but not on biochemical outcome parameters: a review of clinical trials. *BMC Med* 2007;5:3. [\[Context Link\]](#)

171. Kirsch I, Weixel LJ. Double-blind versus deceptive administration of a placebo. *Behav Neurosci* 1988;102:319-23. [\[Context Link\]](#)

172. Price JL. Free will versus survival: brain systems that underlie intrinsic constraints on behavior. *J Comp Neurol* 2005;493:132-9. [\[Context Link\]](#)

173. Pollo A, Vighetti S, Rainero I, Benedetti F. Placebo analgesia and the heart. *Pain* 2003;102:125-33. [\[Context Link\]](#)

174. Petrovic P, Dietrich T, Fransson P, Andersson J, Carlsson K, Ingvar M. Placebo in emotional processing-induced expectations of anxiety relief activate a generalized modulatory network. *Neuron* 2005;46:957-69. [\[Context Link\]](#)

175. de la Fuente-Fernandez R, Schulzer M, Stoessl AJ. Placebo mechanisms and reward circuitry: clues from Parkinson's disease. *Biol Psychiatry* 2004;56:67-71. [\[Context Link\]](#)

176. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta JK. Individual differences in reward responding explain placebo-induced expectations and effects. *Neuron* 2007;55:325-36. [\[Context Link\]](#)

177. Benedetti F, Colloca L, Torre E, Lanotte M, Melcarne A, Pesare M, Bergamasco B, Lopiano L. Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus. *Nat Neurosci* 2004;7:587-8. [\[Context Link\]](#)

178. de la Fuente-Fernández R, Ruth TJ, Sossi V, Schulzer M, Calne DB, Stoessl AJ. Expectation and dopamine

release: mechanism of the placebo effect in Parkinson's disease. *Science* 2001;293:1164-6. [\[Context Link\]](#)

179. Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, Nemeroff CB, Bremner JD, Carney RM, Coyne JC, DeLong MR, Frasur-Smith N, Glassman AH, Gold PW, Grant I, Gwyther L, Ironson G, Johnson RL, Kanner AM, Katon WJ, Kaufmann PG, Keefe FJ, Ketter T, Laughren TP, Leserman J, Lyketsos CG, McDonald WM, McEwen BS, Miller AH, Musselman D, O'Connor C, Petitto JM, Pollock BG, Robinson RG, Roose SP, Rowland J, Sheline Y, Sheps DS, Simon G, Spiegel D, Stunkard A, Sunderland T, Tibbits P Jr, Valvo WJ. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry* 2005;58:175-89. [\[Context Link\]](#)

180. Swanson LW. *Brain Architecture—Understanding the Basic Plan*. New York: Oxford University Press; 2003. [\[Context Link\]](#)

181. Atkinson IC, Renteria L, Burd H, Pliskin NH, Thulborn KR. Safety of human MRI at static fields above the FDA 8 T guideline: sodium imaging at 9.4 T does not affect vital signs or cognitive ability. *J Magn Reson Imaging* 2007;26:1222-7. [\[Context Link\]](#)

182. Barefoot JC, Dahlstrom WG, Williams RB Jr. Hostility, CHD incidence, and total mortality: a 25-year follow-up study of 255 physicians. *Psychosom Med* 1983;45:59-63. [\[Context Link\]](#)

183. Suls J, Bunde J. Anger, anxiety, and depression as risk factors for cardiovascular disease: the problems and implications of overlapping affective dispositions. *Psychol Bull* 2005;131:260-300. [\[Context Link\]](#)

184. Dear P. *The Intelligibility of Nature—How Science Makes Sense of the World*. Chicago: University of Chicago Press; 2006. [\[Context Link\]](#)

185. Frasur-Smith N, Lesperance F. Reflections on depression as a cardiac risk factor. *Psychosom Med* 2005;67:S19-S25. [\[Context Link\]](#)

186. Katon W, Rutter C, Simon G, Lin E, Ludman E, Ciechanowski P, Kinder L, Young B, Von Korff M. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care* 2005;28:2668-72. [\[Context Link\]](#)

187. Onitilo A, Nietert P, Egede L. Effect of depression on all-cause mortality in adults with cancer and differential effects by cancer site. *Gen Hosp Psychiatry* 2006;28:396-402. [\[Context Link\]](#)

188. Jorge RE, Robinson RG, Arndt S, Starkstein S. Mortality and poststroke depression: a placebo-controlled trial of antidepressants. *Am J Psychiatry* 2003;160:1823-9. [\[Context Link\]](#)

189. Langenecker SA, Kennedy SE, Guidotti LM, Briceno EM, Own LS, Hooven T, Young EA, Akil H, Noll DC, Zubieta JK. Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. *Biol Psychiatry* 2007;62:1272-80. [\[Context Link\]](#)

190. Ginsburg GS, McCarthy JJ. Personalized medicine: revolutionizing drug discovery and patient care. *Trends Biotechnol* 2001;19:491-6. [\[Context Link\]](#)

191. Gordon E, Cooper N, Rennie C, Hermens D, Williams LM. Integrative neuroscience: the role of a standardized database. *Clin EEG Neurosci* 2005;36:64-75. [[Context Link](#)]
192. Gordon E, Liddell BJ, Brown KJ, Bryant R, Clark CR, DAS P, Dobson-Stone C, Falconer E, Felmingham K, Flynn G, Gatt JM, Harris A, Hermens DF, Hopkinson PJ, Kemp AH, Kuan SA, Lazzaro I, Moyle J, Paul RH, Rennie CJ, Schofield P, Whitford T, Williams LM. Integrating objective gene-brain-behavior markers of psychiatric disorders. *J Integr Neurosci* 2007;6:1-34. [[Context Link](#)]
193. Volkmann J. Update on surgery for Parkinson's disease. *Curr Opin Neurol* 2007;20:465-9. [[Context Link](#)]
194. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schwalb JM, Kennedy SH. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005;45:651-60. [[Context Link](#)]
195. Greenberg BD, Malone DA, Friehs GM, Rezai AR, Kubu CS, Malloy PF, Salloway SP, Okun MS, Goodman WK, Rasmussen SA. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology* 2006;31:2384-93. [[Context Link](#)]
196. Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatr Scand* 2007;116:165-73. [[Context Link](#)]
197. Sampson SM, Rome JD, Rummans TA. Slow-frequency rTMS reduces fibromyalgia pain. *Pain Med* 2006;7:115-8. [[Context Link](#)]
198. George MS, Nahas Z, Borckardt JJ, Anderson B, Foust MJ, Burns C, Kose S, Short EB. Brain stimulation for the treatment of psychiatric disorders. *Curr Opin Psychiatry* 2007;20:250-4. [[Context Link](#)]
199. Nahas Z, Teneback C, Chae JH, Mu Q, Molnar C, Kozel FA, Walker J, Anderson B, Koola J, Kose S, Lomarev M, Bohning DE, George MS. Serial vagus nerve stimulation functional MRI in treatment-resistant depression. *Neuropsychopharmacology* 2007;32:1649-60. [[Context Link](#)]
200. Engel G. The need for a new medical model: a challenge for biomedicine. *Science* 1977;196:129-36. [[Context Link](#)]
201. Sarter M, Berntson GG, Cacioppo JT. Brain imaging and cognitive neuroscience. Toward strong inference in attributing function to structure. *Am Psychol* 1996;51:13-21. [[Context Link](#)]

Key words: neuroscience; anterior cingulate cortex; emotion; pain; cardiovascular regulation; placebo
