CHAPTER 23

Impact of Functional Visceral and Somatic Pain/ Stress Syndromes on Cingulate Cortex

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Chapter contents

In contrast to many clinical pain syndromes, wherein a medical history and physical examination usually lead to the diagnosis of a structural lesion or biochemical alteration, the functional pain syndromes are without fixed organic peripheral changes. The functional pain disorders include fibromyalgia (FM), atypical facial pain (also termed idiopathic facial pain), non-specific low-back pain (NSLBP), and irritable bowel syndrome (IBS), and are characterized by their persistence, intractability, and apparent absence of peripheral disease. Various psychiatric designations have been applied to pain disorders that are characterized by medically unexplained symptoms: somatization, somatoform disorders, psychogenic disease, chronic multisymptom illness, affective spectrum disorders, and central sensitization syndromes as well as functional disorders (Barsky & Borus, 1999; Clauw & Chrousos, 1997; Clauw *et al.,* 1997; Hudson *et al.,* 1992; Hudson & Pope, 1989; Wessely *et al.,* 1999). A functional disorder is one that, after appropriate medical assessment, cannot be explained in terms of a conventionally defined medical disease based on biochemical or structural abnormalities (Derbyshire *et al.,* 2004; Wessely *et al.,* 1999; Drossman *et al.,* 2000).

Although these disorders are routinely assessed and viewed as separate clinical entities, combining these systemic and regional conditions in a review is justified by several observations: (1) there is considerable overlap in the case definitions of specific syndromes, (2) the disorders co-aggregate in individuals, (3) patients with different syndromes share non-symptom characteristics, (4) the functional syndromes all respond to similar therapies, (5) the syndromes share common neurobiological mechanisms, such as abnormal sensory processing, neuroendocrine, and autonomic dysfunction (Wessely *et al.,* 1999), (6) the disorders have complex etiologies that are best approached with multiple levels of analysis, that incorporate behavior, coping strategies, genetics, prior stressors, and environmental factors with physical mechanisms, and (7) all show some level of altered functioning in the cingulate gyrus.

Functional pain syndromes pose a major challenge to medicine because they are common, persistent, and are associated with significant distress and disability and much unnecessary expenditure of medical resources is associated with conventional therapy (Turk, 2003; Turk & Rudy, 1992; Wessely *et al.,* 1999). There is considerable interest in uncovering the neurobiological bases of these syndromes that might lead to improving therapy (Derbyshire, 1999, 2000; Apkarian *et al.,* 2004). To the extent that functional pain may be associated with impairment of cingulate functions and these impairments account for part of the clinical presentations, therapy directed at cingulate functions could help reduce the cost of their treatment and provide more precise therapeutic targets.

Although pain of unknown origin is a unifying feature of the functional pain disorders, the intensity and intrusiveness of the pain waxes and wanes as do associated psychiatric symptoms like depression and anxiety. As such, their neural substrates may need to be conceptualized in terms of two components: (1) a fixed area of increased vulnerability and (2) areas of more active dysfunction during periods of clinical exacerbation. The plasticity of the clinical symptoms suggest that the neuroanatomical substrates of functional pain may not take the form of traditional neuropathological lesions that may cause central pain and associated disorders (Bowsher, 2005). The plasticity of cingulate function and the well-documented involvement of the anterior cingulate cortex (ACC) in both pain processing and affective disorders suggest the cingulate cortex as a potential area of increased vulnerability for functional pain. Within the past two decades, cingulate function has been investigated with a variety of anatomical and functional brain imaging techniques that promise to uncover cingulate vulnerability to pain.

Goals and Rationale of This Chapter

This chapter reviews the emerging information on the cingulate responses or dysfunction in some of the functional pain and stress syndromes and evaluates cingulate activity in terms of the principles that are covered in other chapters of this book. We focus on three functional pain syndromes, IBS, NSLBP, and FM, as being representative of the entire class. The similarities described above suggest a common clinical course and there is a complex interplay between the functional pain disorders and stress-related mental disorders including depression and post-traumatic stress disorder (PTSD). The functional pain disorders and mental disorders may share a common etiology (e.g., stress, common genetic factor, common neural circuitry), or may be involved in similar etiologies; for example, pain leads to depression, or depression is involved in maintenance of pain after minor injury.

The interpretation of neuroanatomical information based on neuroimaging methods requires caution. Areas of hypo- or hyperfunction may involve either excitatory or inhibitory pathways and may represent either pathological processes or compensatory adaptations triggered by the pathology. Moreover, marked gender and individual differences in the processing of information, as revealed by imaging techniques, show that the range of normalcy is wide. Inferring pathology on the basis of relatively minor or occasional deviations from customary activation patterns is unwise. For these reasons, we offer the initial outlines of a neuroanatomy

for functional pain based on an overview of research completed in the past two decades and consider the co-involvement of important psychiatric cofactors such as depression that have a localized cingulate expression pattern. Each syndrome is considered from the following perspectives:

1 Key symptoms;
2 Neuropsychological studies and potential relationships to cingulate functions;
3 Functional imaging during symptom provocation; and
4 Animal models and circuits that render common points of pain and stress processing that is mediated by cingulate cortex.

Irritable Bowel Syndrome

The IBS accounts for 3% of primary care consultations and as much as half of all consultations to gastroenterologists; it is the most common gastrointestinal disease (Harvey *et al.,* 1983; Mitchell & Drossman, 1987; Spiller, 2005). Gastrointestinal symptoms are strikingly frequent in the general population with 60–70% of people reporting at least one troublesome symptom during the past year (Drossman *et al.,* 1993). The estimated population prevalence of IBS varies from 3 to 22% depending on the criteria used (Boyce *et al.,* 2000; Drossman *et al.,* 1993; Saito *et al.,* 2000). The primary symptoms of IBS are abdominal pain/discomfort, and associated alterations in bowel habits. The cardinal symptom criteria includes the absence of any detectable structural or biochemical abnormalities, which has led to psychosocial factors being increasingly invoked as part of the disease etiology (Drossman *et al.,* 1999). To the extent that psychosocial factors including child abuse and depression reflect disruption of the functions of cingulate cortex, it is probable that cingulate function is altered in IBS. Like other functional syndromes, IBS has been defined negatively as 'symptoms not explained by structural or biochemical abnormalities' and the diagnosis has been determined by symptom criteria (e.g., a change in pain with bowel movement).

It is surprising that we still do not know the extent to which IBS is due to hypersensitivity in the gastrointestinal tract or to altered patterns of activity in the pain neuromatrix. Visceral hypersensitivity is highly prevalent in IBS patients and most also demonstrate wider patterns of somatic referral of intestinal pain or discomfort. A peripheral hypersensitivity may explain IBS symptoms as the sensitive gut can be more easily provoked by normal or abnormal motor events. Several lines of evidence, however, suggest caution before accepting rectosigmoid hypersensitivity as a biological marker of IBS (Camilleri *et al.,* 2001). Firstly, across studies, the prevalence of rectal hypersensitivity in IBS is 20–80% and may only be demonstrable in response to repetitive stimuli rather than single stimuli (Camilleri *et al.,* 2001; Munakata *et al.,* 1997). There is abundant variability in findings even when considering reports from the same group (Verne *et al.,* 2001; Rodrigues *et al.,* 2005). Secondly, there is only a weak correlation between rectal sensory thresholds and current pain, and no significant correlation with pain severity in the prior two weeks (Whitehead *et al.,* 1998). Thirdly, demonstration of rectal hypersensitivity has not yet contributed to the diagnosis or alteration of pharmacotherapy in IBS. Fourthly, rectal hypersensitivity provides a description of IBS (patients have gut related sensitivity) without providing a mechanism for the disease.

One clue to the mechanism of IBS comes from a study of somatic nociception in IBS (Rodrigues *et al.,* 2005). They showed that cutaneous pain sensitivity in IBS patients was raised in the calf, an area with viscero-somatic referred sensitivity, but also in dermatomes distant from those with viscero-somatic convergence, including the face and arms. This is important because it implies that IBS pain may not be directly dependent upon visceral input but is part of a generalized sensitization that must extend beyond the periphery and the region of viscero-somatic convergence in the dorsal horn to include the thalamus and higher cortical centers.

In addition to their abdominal pain, patients with IBS commonly report symptoms such as disturbed sleep and libido and energy reduction (Farrar *et al.,* 2001; Fass *et al.,* 1998; Hudson *et al.,* 1992) as well as headaches, back pain, myalgias and dyspareunia, urinary urgency, and pain (Alagiri *et al.,* 1997; Clauw *et al.,* 1997; Monga *et al.,* 1997). IBS patients share these additional symptoms with other patients such as those suffering atypical facial pain and FM that are also suggested as a consequence of generalized alterations in the processing of viscerosensory information. Patients with IBS have been similarly shown to selectively attend to negative information and to have a memory bias for negative information (Gomborone *et al.,* 1993). Thus the symptoms of IBS are embedded within an altered cognitive and affective structure compared with the symptom free population and common with other functional syndromes.

These findings implicate dysfunction of midcingulate cortex (MCC), which may account for the alterations in cognition, as well as dysfunction of the ACC, which may account for changes in affect, sleep, and energy reduction. Several functional imaging studies have demonstrated altered or dysfunctional activation of the ACC in patients with functional pain (Derbyshire

et al., 1994; Silverman *et al.,* 1997; Naliboff *et al.,* 2001; Verne *et al.*, 2003; Gracely *et al.,* 2004). The results are mixed but generally indicate greater activation of the MCC in functional pain patients during the processing of an acute noxious stimulus and/or during exacerbation of underlying chronic pain symptoms. Visceral pain tends to also include the pregenual ACC (reviewed in Derbyshire, 2003 and the next section).

Neuroanatomy of Functional Pain: Visceral Syndromes

Functional imaging techniques have been used to investigate brain responses to noxious stimulation and the cerebral networks that participate in normal somatic and visceral pain perception (Derbyshire, 1999, 2000, 2003; Peyron *et al.,* 2000; Bremner, 2005). A principle that emerges from the many imaging assessments during acute nociceptive stimulation is that MCC is a consistent participant in the pain neuromatrix. Furthermore, these same techniques have been applied to patients suffering functional somatic and visceral disorders and these studies suggest impairment of cingulate cortex. These latter findings, however, remain preliminary and they are often contradictory, most likely because of the complex nature of the peripheral and central disease and wide variability in the characteristics of the patient populations.

The experience of visceral sensation is diffuse whereas somatic sensation is quite precise. There are clearly different peripheral receptor systems involved and quite possibly different anatomical pathways including the ascending spinothalamic and descending noxious inhibitory systems. Nevertheless, functional disorders of the somatic system like FM have diagnostic overlap with functional disorders of the visceral system such as IBS and brain activation patterns in response to visceral and somatic stimuli are therefore likely to show similar features as well as areas of difference.

Activation during visceral stimulation includes the pregenual ACC (pACC) and anterior MCC (aMCC); however, activation during somatic sensation in somatic pain syndromes is restricted to MCC, considered further below. Kern *et al.* (2004) stimulated the esophagus with acid to induce heartburn in gastroesophageal reflux disease (GERD) patients and Naliboff *et al.* (2001) and Mayer *et al.* (2005) employed noxious rectal distension in IBS patients. All three studies activated pACC. Verne *et al.* (2003) used noxious rectal distension in IBS patients and activated a region posterior to the first two studies in aMCC but not the pACC.

Naliboff *et al.* (2001) used preconditioning with repetitive sigmoid distension. Rapid repetitive distension of the sigmoid colon sensitizes the rectal region and is likely to provide unique patterns of activation. Thus, it could be that the sensitization of the organ is the important event driving pACC activity. In support of this suggestion, Lorenz & Casey (2005) reported activation of the pACC following heat stimulation in skin previously sensitized with capsaicin. Application of acid in the esophagus is also a sensitizing event (Sarkar *et al.,* 2000).

The pregenual areas 24 and 32 and subgenual area 25 receive substantial direct input from the amygdala and some from the hypothalamus, while area 25 projects to the nucleus of the tractus solitarus (NTS) and all parts of ACC project to the PAG. This circuitry represents a system capable of mediating important autonomic visceral responses, affective integration of visceral events, and descending modulation of viscerosensory traffic. It is not surprising, therefore, that this region of cingulate cortex is more engaged during visceral than somatic sensation (Derbyshire, 2003; Chapter 10). The majority of cingulate activation in patients with functional pain, from either visceral or somatic sources, however, lies at the border of the aMCC) and posterior MCC (pMCC). We have proposed this subdivision of MCC based on several lines of evidence, including structural cytoarchitecture, functional, and connectional differences (Vogt *et al.,* 2003). For example, the amygdala projections into the pACC extend into aMCC but not pMCC. There is also a relatively higher density of opioid receptors in aMCC than pMCC, similar to pACC (Chapter 15). In addition, aMCC and not pMCC is the region demonstrated by Rainville *et al.* (1997) and Faymonville *et al.* (2000; Chapter 17) to activate in proportion to the degree of experienced unpleasantness and was exclusively activated during pain experience compared with performing the Stroop task (Derbyshire *et al.,* 1997).

The ACC and adjacent structures play a critical role in regulation of peripheral neurohormonal responses to stress (Feldman *et al.,* 1995). In addition to the amygdala and the hypothalamus, portions of the medial prefrontal cortex project to the NTS and nucleus ambiguus in the brainstem where they regulate heart rate and blood pressure responses to stress. Lesions of the pACC resulted in increased heart responses to conditioned stimuli, suggesting that this region decreases heart rate response to stress, while lesions in the ventral portion decreased heart response, suggesting that this region increases heart rate response to stress (Frysztak & Neafsey, 1994). Lesions of the ACC are associated with a blunted cortisol and adrenocorticotrophic hormone response to stress, with no effect on resting cortisol (Diorio *et al.,* 1993). Thus, dysfunction of the ACC in functional pain syndromes may play a role in maintaining symptoms in multiple ways, either through modulation of pain sensitivity, emotion, or peripheral hormonal responses to stress.

Fibromyalgia

Population surveys suggest that 5% of women and <2% of men suffer from FM (White *et al.,* 1999). Typically, FM patients complain of chronic widespread pain involving all four quadrants of the body as well as the axial skeleton with a few prominent tender points, diffuse tenderness, fatigue, and sleep disturbance (Wolfe *et al.,* 1990). Until fairly recently, it was assumed either that local pathology would explain the patient's distress or that the pain was to be explained by psychocultural factors alone (Croft, 2000). This view has now largely given way to an understanding of FM symptoms as a clinical syndrome in their own right with a complex and multifactorial etiology that is not completely understood. FM diagnostic criteria require at least 3 months of widespread pain and pain upon digital palpation at no fewer than 11 of 18 characteristic tender points.

The critical link between FM and stress syndromes is emphasized by the fact that PTSD is highly comorbid. More than 50% of FM patients experience PTSD compared with only 6% in the general population (Sherman *et al.,* 2000). Indeed, traumatic events are usually perceived as life threatening and can lead to emotional responses including horror, helplessness, or fear. These responses together can lead to increased somatic complaints, including pain, and FM is increased to 21% in PTSD (Amir *et al.,* 1997). Finally, neurohormonal responses in FM are similar to those in PTSD with sufficient baseline activity but impaired stress responses (Staud, 2004).

Unconstrained by the need to describe local pathology, pain research has provided a model of FM based upon early activation or greater activation of central regions responsible for pain experience. The known relationship of stress and negative affect to 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 FM symptoms (Gracely *et al.,* 2002, 2004). Recently, it has been demonstrated that catastrophization—focusing upon the most negative outcomes associated with pain—in patients with FM is correlated with enhanced activation of the dorsal cingulate (Gracely *et al.,* 2004). As for IBS, the persistence of FM symptoms in the absence of identifiable peripheral pathology has led to increased use of functional imaging to uncover abnormalities with an expected focus in the ACC.

One possible mechanism of central dysfunction in FM is impairment in the descending noxious inhibitory system. Julien *et al.* (2005) used a noxious cold water bath to stimulate eight segments of the arm in an ascending or descending fashion. They observed sensitization in control and chronic low-back pain patients but no differences in the FM group. Their interpretation that the FM patients have a deficit in the descending noxious inhibitory system has specific implications for the involvement of cingulate cortex in FM. Indeed, the pACC has the most robust projection to the periaqueductal gray, while the aMCC has a lesser projection and the pMCC has least (Faymonville *et al.,* Chapters 15 and 17).

Neuroanatomy of Functional Pain: FM

Although the total number of studies is still limited, as a general rule, the functional somatic pain syndromes activate MCC rather than ACC. In terms of FM, Figure 23.1 shows that Gracely *et al.* (2004) used noxious stimulation of the left thumb with pressure in catastrophizing FM patients to activate pMCC encroaching onto the posterior part of aMCC. In another study by Gracely *et al.* (2002), noxious stimulation of the left thumb with pressure in FM patients generated activity in pMCC and dPCC. Chang *et al.* (2003) also demonstrated increased aMCC activation in patients with combined FM and IBS during pressure pain relative to a group of patients with IBS alone. Taken together, these findings imply a slight anterior shift in MCC activation in patients with greater distress due to their FM pain.

Non-specific Low-Back Pain

Back pain is the second leading symptomatic reason for physician visits in the United States (Lemrow *et al.,* 1990). As with FM and IBS, there is a lack of observable pathology to account for NSLBP, treatment is difficult, and there is an uncertain association with affect and illness behavior (Fordyce, 1995). Jensen *et al.* (1994) have demonstrated that subjects with NSLBP have similar levels of lower back pathology to normal controls matched for age and sex. We have also demonstrated that controls significantly younger than NSLBP patients have comparable incidence of lumbar pathology including disk herniation (Derbyshire *et al.,* 2002) and a further group have demonstrated that structural abnormalities observed on MR scans do not predict the subsequent development or duration of low-back pain (Borenstein *et al.,* 2001). The best evidence suggests that fewer than 15% of persons with back pain can be assigned to a category of specific low-back pain with identifiable cause and treatment (Spitzer *et al.,* 1987). This leaves a substantial proportion of people suffering back pain without reliable indicators of injury or a physiological or anatomical defect (Hadler, 1994).

The persistence, intractability, and apparent absence of spinal abnormality to account for NSLBP has led to an increasing interest in the possibility that the pain

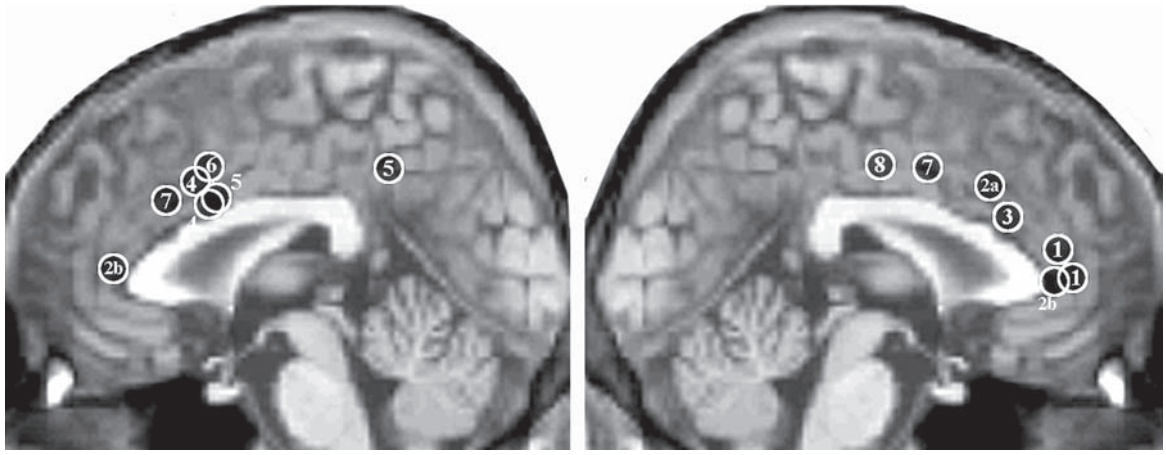

Fig. 23.1 Activation sites during visceral or somatic stimulation in patients with functional pain. Functional visceral populations include: 1. Kern *et al.* (2004) acid induced heartburn in GERD patients; 2. Naliboff *et al.* (2001) noxious rectal distension in IBS patients (2a before repetitive distension of the sigmoid colon, 2b after); 3. Verne *et al.* (2003) noxious rectal distension in IBS patients. Functional somatic populations include: 4. Gracely *et al.* (2004) noxious left thumb pressure in catastrophizing FM patients; 5. Gracely *et al.* (2002) noxious left thumb pressure in FM patients; 6. Giesecke *et al.* (2004) noxious left thumb pressure in NSLBP patients; 7. Derbyshire *et al.* (2002) noxious heat to the right hand in NSLBP patients; 8. Derbyshire *et al.* (1994) noxious heat to the right hand in AFP patients.

is a consequence of stress or a variation of affective disorders similar to other functional pains (Barsky & Borus, 1999; Wessely *et al.,* 1999). Consequently, interventions for NSLBP often attempt to modify the patient's thoughts about pain and their mood (Woby *et al.,* 2004; McCracken & Eccleston, 2005). Pain-related fear, pain intensity, pain catastrophizing, daily stress, depression, and anxiety have all been shown to impact negatively upon quality of life, disability, and pain experience (Severeijns *et al.,* 2001; Pincus *et al.,* 2002; Blackburn-Munro & Blackburn-Munro, 2001). Currently, there is little research placing these observations into a neuroanatomical framework, although alterations in motor behavior (disability), increases in cognitive load (catastrophizing), and the changes in affect could all be explained by alterations in cingulate function, only Gracely *et al.* (2004) have demonstrated altered activation of the ACC in catastrophizing FM patients.

A further clue to the neural contribution to NSLBP, however, comes from studies by Bruehl *et al.* (2002, 2003). They demonstrated that NSLBP patients that readily express their anger (anger-out patients) have reduced opioid analgesia. Their results provide preliminary support for a positive association between anger expression and chronic pain intensity mediated by opioid antinociceptive system dysfunction. Previous studies have demonstrated involvement of the aMCC during anger (Vogt *et al.,* 2003), a region that has high opioid receptor density (Vogt *et al.,* 1995; Chapter 15).

Neuroanatomy of Functional Pain: NSLBP

Two studies have applied noxious cutaneous stimulation to the skin of patients with NSLBP during functional imaging (Giesecke *et al.,* 2004; Derbyshire *et al.,* 2002). Both studies applied an additional noxious source so as to compare the brain activation of patients with comparable responses in a control group. Both studies delivered comparable levels of noxious stimulation to control subjects and to patients. Giesecke *et al.* delivered pressure to the right thumbnail, while Derbyshire *et al.* delivered heat to the right hand. Giesecke reported the need for significantly greater pressure in control subjects to provide comparable pain experience to that of the patients whereas Derbyshire reported significantly greater pain experience in patients when using the same heat stimulus. Despite these similarities, Giesecke found greater levels of activation across the pain neuromatrix when applying comparable pressure but Derbyshire found only minimal differences in activation when delivering the same heat intensity. The most obvious explanation for such different findings is that the patients in Giesecke's study experienced more pain than the patients in Derbyshire's study, although this is difficult to verify because Giesecke reported categorical pain rather than continuous scores on a visual analogue scale (VAS). While greater pain in the Giesecke study providing for greater brain activation appears a reasonable interpretation, there is a deeper puzzle. Several reviews have generally reported reduced brain activation in a

variety of chronic pain patients undergoing several different noxious stimulation procedures (Derbyshire, 1999; Peyron *et al*, 2000; Apkarian *et al.,* 2005). The results of Giesecke, generally augmented brain response in patients relative to controls, and those of Derbyshire, generally similar responses relative to controls, therefore, both are out of step with the body of data suggesting generally attenuated responses relative to controls.

These discrepancies point to the capricious nature of functional imaging experiments into pain. Data from individual subjects is not often included in reports but, where it has been, a startling degree of subject to subject variability in brain responses to pain is apparent (Vogt *et al.,* 1996; Davis *et al.*, 1997; Kwan *et al.*, 2000). The basis of this variability remains largely unknown but it is a reasonable hypothesis that variation in brain activation during pain is related to variation in the psychological parameters that are known to influence chronic pain experience: pain-related fear, pain intensity, pain catastrophizing, daily stress, depression, and anxiety. These parameters have a substantial and well-documented influence upon chronic pain experience and so may influence variability across studies of chronic pain even more than studies of acute pain in normal volunteers. These speculations will be addressed in subsequent sections.

Overlap of Functional Pain and Stress

The hypothalamic–pituitary–adrenal (HPA) axis plays an important role in the stress response (McEwen, 1998). Activation of the hypothalamus leads to the secretion of corticotrophin from the pituitary and releases catecholamines from the adrenal medulla and corticotrophin, in turn, mediates the release of cortisol from the adrenal cortex. Frequent stress, poor adaptation to stress, and congenital factors can act individually or in combination to maintain activation of the HPA axis. Continuous activation of the HPA axis can have negative effects including exhaustion of the system and damage to neural structures. A vulnerable link in the regulation of the HPA axis is the hippocampal region (Sapolsky, 1996), which has high concentrations of cortisol receptors. Continuous circulation of cortisol (Sapolsky, 1996) and CRF (Brunson *et al.,* 2001) leads to the destruction of hippocampal cells and further dysregulates the HPA axis as well as cognition. Stress can directly interfere with hippocampal-based mechanisms of memory function, including long-term potentiation (Diamond *et al.,* 1996); studies have also shown that stress is associated with an inhibition of neurogenesis (or the growth of new neurons) in the hippocampus (Gould *et al.,* 1998).

The central nervous system effects of chronic stress are reversed with antidepressants (Duman *et al.,* 2001) and antiepileptics (Czeh *et al.,* 2001; Watanabe *et al.,* 1992); in fact, neurogenesis may be required for the behavioral effects of antidepressants to occur (Santarelli *et al.,* 2003). Animal studies have also shown that stress is associated with a decrease in neuronal branching in the ACC (Raudley *et al.,* 2004). Magnetic resonance imaging has shown that stress-related disorders such as recurrent depressive illness and PTSD are associated with atrophy of the hippocampus (Bremner *et al.,* 1995; Sheline *et al.,* 1996; Bremner *et al.,* 2000); these effects are reversible with antidepressant (Vermetten *et al.,* 2003) or antiepileptic treatment (Bremner *et al.,* 2005).

Although hippocampal dysfunction can account for some of the deficits in memory performance reported by patients with depression and PTSD, other symptoms suggest cingulate cortex damage. The restricted range of affect, rumination, diminished interest or participation in activities, hypervigilance towards sources of threat and irritability, and anger suggest a broader involvement of the cerebral cortex in general and the ACC in particular. For example, long-term memories of negative events associated with PTSD are stored in sACC, not the hippocampus, and reduced ACC volume has been reported in patients with PTSD (Yamasue *et al.,* 2003). For a full review of the involvement of ACC in PTSD, see Chapter 21.

Increased levels of CRH or glucocorticoids also result in enhanced firing of midbrain serotonergic raphe neurons, which may play a role in stress-mediated analgesia. As stress becomes chronic, this may lead to depletion of central serotonin, up-regulation of the brainstem presynaptic 5-HT1A receptor, and glucocorticoid-induced down-regulation of the post-synaptic hippocampal 5-HT1A receptor (Mendelson & McEwan, 1991; McKittrick *et al.,* 1995; Wu *et al.,* 1999). Such events could lead to symptoms of depression and anxiety (Petty & Sherman, 1983). Depletion of central serotonin might also lead to an increase in ascending nociceptive transmission, associated with either peripheral inflammation or neuropathic injury, as activation of dorsal horn projecting serotonergic neurons in the rostroventral medulla generally attenuates ascending nociceptive transmission.

The functional pain disorders have not been shown to share all the neurobiological alterations found in stress-related psychiatric conditions like depression and PTSD. Importantly, hippocampal activity is rarely observed in control subjects experiencing pain or in functional pain patients (Derbyshire, 1999; 2000; Farrell, 2005) and reduced hippocampal volume has not been reported in patients with long-standing chronic pain (Apkarian *et al.,* 2004). These observations suggest that functional pain disorders are not purely stress-related conditions. Although rates of exposure to

traumatic stress like childhood abuse are higher than in the general population, not all patients with functional pain syndromes have histories of exposure to traumatic stress, even after close examination. Some patients do indeed have histories of severe stress, such as being continuously abused mentally or physically or being involved in combat, and in these cases stress has been suggested to have a causal relationship with functional pain syndromes (Drossman *et al.,* 1996). More commonly, however, a patient may report a single precipitating source of stress, such as vehicle accident, and/or a period of general psychological disturbance and malaise (Madland & Feinmann, 2001; Feinmann & Harris, 1984). For these patients, the source of continual stress is the disorder itself, which is mediated through their cognitions about pain, self and their affective state (Fernandez & Turk, 1992, Turk & Rudy, 1992). Some have hypothesized that these physical traumas can lead to an increased general neuronal hypersensitization, leading to a generalized increased sensitivity, which manifests itself in different ways in different individuals (e.g., multiple sensitivity points in FM, or increased sensitivity to one's own bowel contractions in IBS). Thus, it is likely that the experience of functional pain will involve disturbance in higher cortical centers including the cingulate gyrus that process both cognition and affective states.

Depression Influences Cingulate Pain Processing

There are many significant associations between depressive symptoms and the experience of chronic pain disorder with over half of clinically depressed patients also reporting pain (Merskey, 1986; Lepine & Briley, 2004). Subjects with depression have been reported as 3–7 times more likely to develop multiple physical symptoms than non-depressed subjects and even mild symptoms of depression are associated with twice the normal level of chronic painful conditions (Hotopf *et al.,* 1998; Ohayon & Schatzberg, 2003). Depression can clearly augment the functional impairment associated with pain and increases healthcare utilization even at low levels (Hotopf *et al.,* 1998; Ohayon & Schatzberg, 2003; Gureje *et al.,* 2001).

Whether depression and chronic pain are comorbid states or causally linked remains uncertain (Gureje *et al.,* 2001; Hendler, 1984; Magni *et al.,* 1994; Turk *et al.,* 1995; Blackburn-Munro & Blackburn-Munro, 2001; Ahles *et al.,* 1987). There are at least five major hypotheses regarding the linkage of pain and depression: (1) the 'antecedent hypothesis,' in which depression precedes the development of chronic pain, (2) the 'consequence hypothesis,' in which depression is a consequence of chronic pain, (3) the 'scar hypothesis,' in which episodes of depression occurring before the onset of chronic pain predispose the patient to a depressive episode after the onset of pain, (4) the 'cognitive mediation' hypothesis, in which psychological factors such as poor coping strategies are considered to mediate the reciprocal interactions between chronic pain and depression, and (5) the 'independent hypothesis,' in which depression and chronic pain are considered to share some common neurogenetic mechanisms but remain distinct diseases without causal interaction.

Causal interaction would be supported by evidence that pain processing, anxiety, and depression impact common brain areas and neurotransmitter systems. To explore this possibility, we divided 32 subjects that have been studied in our laboratory over the past ten years, according to their score on the hospital anxiety and depression (HAD) scale (Zigmond & Snaith, 1983). The HAD is a short self-report screening tool that was developed to indicate anxiety and depressive states in patients with physical illness (Herrmann, 1997) and is routinely completed as part of our studies (Derbyshire *et al.,* 1994; 2002). It consists of 14 items to be rated on a four point scale (0–3) with the depression subscale consisting of seven items (e.g., 'I look forward with enjoyment to things'). It has good internal consistency and reliability (Spinhoven *et al.,* 1997; Johnston *et al.,* 2000). The HAD provides a depression score between 0 and 21 with 0 indicating no evidence of depression and 21 maximal evidence of depression. Scores of 0–7 are considered normal, with 8–10 borderline, 11–14 moderate and 15 or over indicating clinical depression (Barczak *et al.,* 1988; Zigmond & Snaith, 1983).

A median split resulted in a group of subjects with some depressive symptoms (n=16, mean HAD depression score=6), and a group of subjects with almost no depressive symptoms (n=16, mean HAD depression score=1.5). The central responses of all subjects to an increasing, intermittent ramp of non-noxious and noxious heat were measured using positron-emission tomography (PET). All the thermal stimuli were produced by a Somedic thermal threshold stimulator described in detail elsewhere (Fruhstorfer *et al.,* 1976). Twelve measures of regional cerebral blood flow (rCBF) were obtained from each of the thirty-two subjects by recording the distribution of cerebral radioactivity following an intravenous bolus infusion of the freely diffusible positron emitting ^{15}O-labeled tracer, H_2O^{15}. For each measurement, individuals received 12 mCi bolus of H_2O^{15} through an automated injector. Four measures were obtained during noxious heat stimulation described as moderately painful, four during mild pain and four during non-noxious heat stimulation. Pain ratings were recorded immediately following each rCBF acquisition as described in detail elsewhere

(Derbyshire *et al.,* 2002). The object of the analysis of these studies was to correlate the changes in rCBF with increasingly painful heat stimulation and to assess the modification of this relationship by depression.

Figure 23.2 shows the results of this analysis. The ACC activity is attenuated in the subjects with high depressive symptoms relative to those without depressive symptoms. More broadly, the medial surface activation patterns for the depressed subjects are strikingly similar to those observed with low sensitivity subjects reporting minimal pain during intense thermal stimulation (Coghill *et al.,* 2003). The subjects with depressive symptoms in the current study, however, reported similar pain as the non-depressed subjects across the range of temperatures delivered. The attenuated response cannot, therefore, be attributed to low pain sensitivity of the depressed subjects. It is the presence of depressive symptoms, rather than reduced sensitivity, which is critical to explaining the attenuated response.

Cingulate Inactivation during Depression

One test of any neurobiological model of structure/function associations is the extent to which cortical units are selectively vulnerable to neuronal diseases. Studies of functional pain syndromes suggest that the aMCC subregion is uniquely involved in both somatic and visceral pain and may therefore be a site of common dysfunction. Functional pain patients share characteristic distress patterns including depression. If this distress is causally involved in the etiology or continuation of functional pain then further selective altered aMCC activation during depression and/or stress might be expected. In Figure 23.2 we demonstrate reduced aMCC in subjects with mild depressive symptoms during acutely noxious stimulation and this hypothesis is assessed further in Figure 23.3.

Most changes in depressed patients occur in subgenual ACC (area 25), which is very rarely involved during pain processing in patients or controls. These findings suggest an important functional difference between pACC area 24 and subgenual area 25 despite sharing some connections and functions relating to autonomic control. There is some evidence of aMCC involvement during transiently induced sadness and anxiety in control subjects as well as during chronic depression in patients and anxiety in non-PTSD Vietnam veterans. These changes largely involved reduced blood flow or FDG uptake rather than increases. Similar to the degeneration observed in the hippocampus in PTSD patients and, more rarely, in the pACC in depressed subjects, it is possible that continuous pain activation of the aMCC weakens the region and leads to later inactivation and the experience of depression (the "scar" hypothesis). Alternately, continuous depression or sadness may attenuate normal responses in this region and disrupt

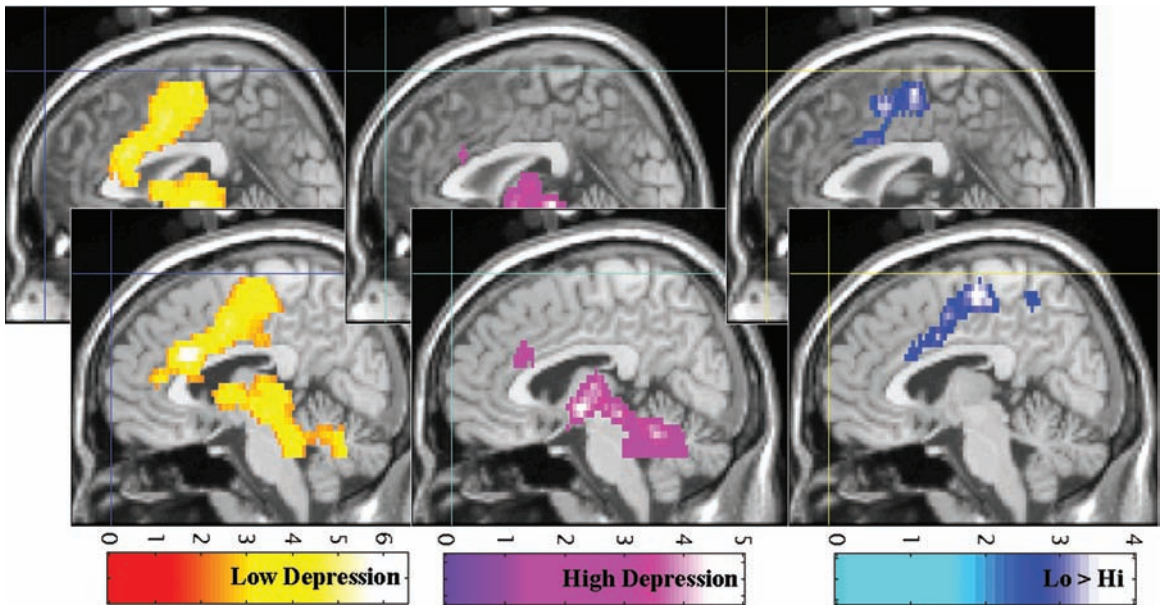

Fig. 23.2 Medial cortical changes in pain related activity (rCBF), 2mm (back) and 6mm (front) to the right of the midline, in the non-depressed subjects (orange-yellow scale), depressed subjects (purple-pink scale) and the differences (blue scale). Increased activation for the non-depressed group in the ACC is significantly attenuated in the presence of depression.

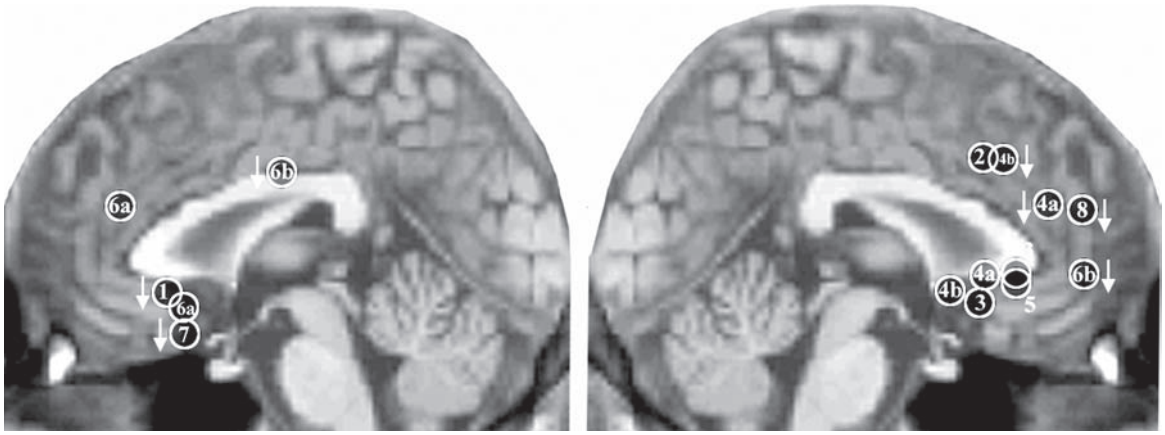

Fig. 23.3 Activations during transient sadness, depression or stress in patients and controls (down arrow indicates negative regional response or deactivation). 1. Drevets *et al.* (1997) bipolar depressed and unipolar depressed patients compared with controls; 2. Gemar *et al.* (1996) male control subjects recalling a sad event; 3. George *et al.* (1995) healthy females recalling sad events while looking at sad faces; 4. Mayberg *et al.* (1999) healthy females recalling sad events (4a) and depressed male patients after successful treatment compared with before treatment (4b); 5. Liotti *et al.* (2002) female control subjects recalling sad events; 6. Bremner *et al.* (1999) male Vietnam veterans with (6b) and without (6a) PTSD experiencing combat related images and sounds; 7. Fischer *et al.* (1998) one female control experiencing an unexpected panic attack; 8. Bishop *et al.* (2004) control subjects presented with infrequent threat stimuli.

descending inhibition of pain exacerbating or causing a functional pain syndrome (the "antecedent" hypothesis). This would suggest that aMCC activation to pain should show an inverse relationship to the length of time a person has suffered chronic functional pain, similar to the reductions observed in prefrontal cortex (Apkarian, 2004, 2005). Most studies, however, suggest that ACC responses to pain are generally augmented relative to controls (Gracely *et al.,* 2002, Derbyshire *et al.,* 1994) or remain similar relative to control subjects (Derbyshire *et al.,* 2002 Apkarian *et al.,* 2005). Interactions with stress or depression, however, which may better model the clinical situation, have not been explored in an imaging environment. Figure 23.2 shows preliminary evidence that depressive symptoms can attenuate normal ACC responses during painful events.

Animal Models and Links between Pain and Stress Syndromes

The human stress literature approaches stress in two parallel and generally unrelated pathways; one associated with cerebral cortical responses as supported in the functional imaging literature and a second hormonal approach mediated via the HPA axis. These stress substrates likely do not operate in isolation, chronic pain likely drives some stress syndromes, and these associations can only be examined with experimental animal models. Thus, primary hypotheses include the following considerations: (1) chronic pain can drive stress syndromes and lead to complex interactions in patient populations, (2) the most likely linkage between cortical stress and HPA systems is a direct projection from ACC to the hypothalamus. Although the paraventricular hypothalamic nucleus (PVN) that mediates the HPA response does not receive direct cortical inputs (Armstrong, 2004), it does receive an input from the lateral hypothalamus (LH) to which the ACC projects (below); and (3) to the extent that chronic pain can induce stress and depression, a direct linkage between pain and stress is possible in ACC and possibly MCC.

One stress model is unavoidable electrical footshock in rodents. Sawchenko *et al.* (2000) showed an increase in the immediate early gene for cFos in areas 25 and 32 in this paradigm; an effect that was not matched by injections of interleukin-1. Rosene *et al.* (2004) showed that cFos activation of a similar part of ACC during restraint stress in rats is enhanced by malnutrition and it appears to be relatively specific to cingulate cortex; i.e., the hippocampus and other regions do not show similar effects.

Interestingly, the ACC does not appear to project directly to the PVN which mediates the stress response but rather to the LH. Kita & Oomura (1981) showed that medial prefrontal cortex including areas 25 and 24 project to the LH and electrical stimulation in this cortical region evokes excitatory/inhibitory and pure inhibitory responses; 44% of the latter were consistent with monosynaptic inhibition. Since projections of the LH to the PVN have been reported (Berk & Finkelstein, 1982) and they might be glutamatergic (Csaki *et al.,* 2002),

the likely intermediate projection in this system linking the ACC and PVN responses is via an excitatory projection of LH to the PVN. A similar projection of ACC, mainly from area 25, to the LH has been shown in the cat (Room *et al.,* 1985) and monkey (Chiba *et al.,* 2001). Finally, restraint stress increases cFos activity in the PVN (Figueiredo *et al.,* 2003). These findings together suggest a two neuron excitatory chain between the ACC and PVN which is activated preferentially during restraint and footshock induced stress but not by cytokine challenge.

Electrical stimulation studies support a mediation of hypothalamic functions by ACC. Thus, stimulation of subgenual ACC (area 25) reduces heart rate, while area 32 and possibly aMCC, increase heart rate. Burns & Wyss (1985) showed that the largest hypotensive responses were evoked from area 25 in anesthetized rats and Fisk & Wyss (2000) injected lidocaine into the lateral hypothalamus during this stimulation and reported reductions during block of the LH.

Since almost no primate studies of stress are available, the transition from understanding rodents to human stress responses is difficult; particularly since a large amount of the primate cingulate gyrus does not have equivalent structures in the rodent brain (Vogt *et al.,* 2004). Nevertheless, an important study is available in the rhesus monkey. Rilling *et al.* (2001) showed that maternal separation was associated with elevated plasma cortisol and this was negatively correlated with blood flow in aMCC (mainly area a24c') measured with [F^{18}]-fluorodeoxyglucose PET. A positive correlation with plasma cortisol was observed in dPCC (possibly area 23c). Since the group comparisons did not show alterations in cingulate cortex and the correlational changes were part of a wider range in prefrontal and visual activity patterns, the specific role of cingulate cortex in the stress response to maternal separation is not known. Nevertheless, the strong correlations between plasma cortisol and specific cingulate cortical areas during maternal separation suggest an important strategy for studying the mechanisms of stress alterations of cingulate function.

Cingulate Links to Visceral and Somatic Pain and Stress Syndromes

It is apparent that the cingulate activation in patients with stress or psychiatric disorder often includes the subgenual area 25 that is largely absent when studying patients with functional pain. In addition, stress disorders, such as PTSD, often involve dysfunction of the hippocampus, which is generally not the case for functional pain patients. Activation in patients with functional pain can involve the pregenual ACC (area 24) when the source of noxious experience involves the lower GI tract but the MCC is commonly activated for both somatic and visceral sources of functional pain. The MCC is also activated or deactivated in patients with psychiatric disease though less often than area 25. These findings suggest a pACC locus for visceral functional pain and stress with psychiatric disease, while somatic pain and stress syndromes are more likely to locate within the MCC also with psychiatric symptoms. In support of this, we have demonstrated reduced activation of the MCC during noxious stimulation in subjects with minor depressive symptoms, replicating our previous findings with depressed patients (Derbyshire & Jones, 1998). MCC is important in the affective and cognitive dimensions of pain experience that are amplified in functional pain patients and is a likely site of negative interaction during functional pain, as has been suggested elsewhere (Drossman *et al.,* 2003).

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