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REVIEW ARTICLE

Brain–gut connections in functional GI disorders: anatomic and physiologic relationships

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Abstract *Understanding the neural regulation of gut function and sensation makes it easier to understand the interrelatedness of emotionality, symptom-attentive behavior or hypervigilance, gut function and pain. The gut and the brain are highly integrated and communicate in a bidirectional fashion largely through the ANS and HPA axis. Within the CNS, the locus of gut control is chiefly within the limbic system, a region of the mammalian brain responsible for both the internal and external homeostasis of the organism. The limbic system also plays a central role in emotionality, which is a nonverbal system that facilitates survival and threat avoidance, social interaction and learning. The generation of emotion and associated physiologic changes are the work of the limbic system and, from a neuroanatomic perspective, the 'mind-body interaction' may largely arise in this region. Finally, the limbic system is also involved in the 'top down' modulation of visceral pain transmission as well as visceral perception. A better understanding of the interactions of the CNS, ENS and enteric immune system will significantly improve our understanding of 'functional' disorders and allow for a more pathophysiologic definition of categories of patients currently lumped under the broad umbrella of FGID.*

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INTRODUCTION

Functional gastrointestinal disorder (FGID) comprises a major portion of clinical practice for gastroenterologists and primary care physicians. Psychosocial disturbances are present in many patients with FGID and are increasingly prevalent in referral populations. Psychosocial factors can influence digestive function, symptom perception, illness behaviour and outcome. Conversely, visceral pain can affect central pain perception, mood and behaviour.[1,2] The combined functioning of gastrointestinal intestinal motor, sensory and CNS activity is termed the brain–gut axis and FGID can be conceptualized as resulting at least in part from dysregulation of the brain–gut axis.[2] This review will explore the relationship between the CNS and the gut to provide the reader with an understanding of gut–brain neurophysiology, which forms the basis for understanding the relevance of the biopsychosocial model of illness as it relates to irritable bowel syndrome (IBS) and other FGID.

BRAIN–GUT AXIS: NEUROANATOMY

Communication between the central nervous system (CNS) and enteric nervous system (ENS) involves neural pathways as well as immune and endocrine mechanisms.[3] Within the CNS, the hypothalamus, an older midbrain structure, plays a central role in maintaining physiological homeostasis of the organism and

regulating autonomic and neuroendocrine function.[4] The hypothalamus forms an integral part of the limbic system, a region of the mammalian brain regarded as the 'visceral' or 'emotional' brain. In addition to its role in regulating homeostasis of the organism, the limbic system functions to mediate emotional responses.[5] An overview of the relationship between the 'emotional nervous system', higher level cortical inputs and the enteric nervous system is shown in Fig. 1.

Anatomically the limbic system consists of the hypothalamus, amygdala, medial thalamus and anterior cingulate cortex (ACC) (Fig. 2). The primary functions and connections of these structures are outlined in Table 1 and only major functions in humans will be discussed here.

The amygdala plays a central role in processing social signals of emotion (such as posture and facial expression), in emotional conditioning (the association of an emotions with a given stimulus) and in the consolidation of emotional memories.[6] In humans, damage to the amygdala results in loss of conditioned fear responses.[7,8] A direct thalamo-amygdala pathway processes crude sensory aspects of incoming stimuli and allows an early conditioned fear response if any of these crude sensory elements are signals of threat. A thalamo-cortico-amygdala pathway that allows more complex analysis of the incoming stimulus and delivers a slower, conditioned emotional response.[9–11]

The ACC integrates visceral, attentional and emotional information and regulates affect.[12,13] The ACC also plays a role in the conscious representation of emotional experience and autonomic arousal.[14–16] The ACC monitors conflict between the functional state of the organism and any new information that has potential affective or motivational consequences.[6] When such conflicts are detected, the ACC projects information about the conflict to areas of the prefrontal cortex (PFC) where adjudications among response options can occur. The ACC consists of a dorsal 'cognitive' subdivision and a ventral 'affective' subdivision (also called the perigenual ACC or pACC[12]. The pACC is routinely activated in functional imaging studies involving all types of emotional stimuli.[6] Current thinking suggests that it monitors conflict between the functional state of the organism and any new information that has potential affective or motivational consequences.[12]

The PFC is a neocortical region involved in affective processing.[17] Its central role is to maintain the representation of goals and the means to achieve them.[18] Particularly in situations that are ambiguous, the PFC signals other areas of the brain to facilitate the expression of task-appropriate responses in the face of

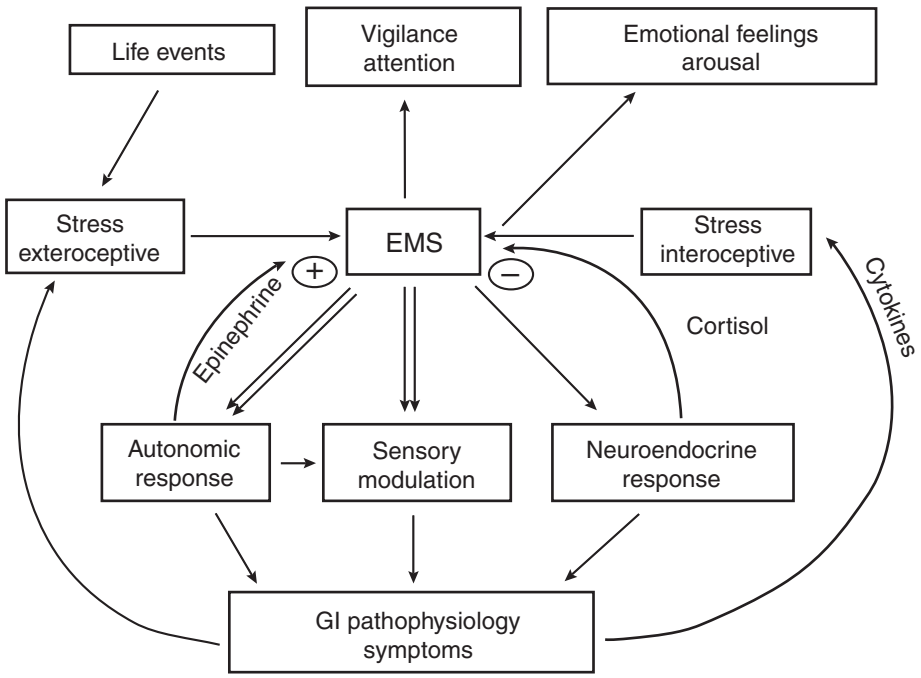

Figure 1 Inputs and outputs of the emotional motor system (EMS). Output pathways of the EMS are activated by psychosocial (exteroceptive) and physical (interoceptive) stressors. Major outputs to the periphery are autonomic, pain modulatory and neuroendocrine responses. An important output to the forebrain occurs in terms of attentional and emotional modulation. Feedback from the gut to the EMS occurs in form of neuroendocrine (epinephrine, cortisol) as well as visceral afferent mechanisms. From Mayer *et al.*[96]

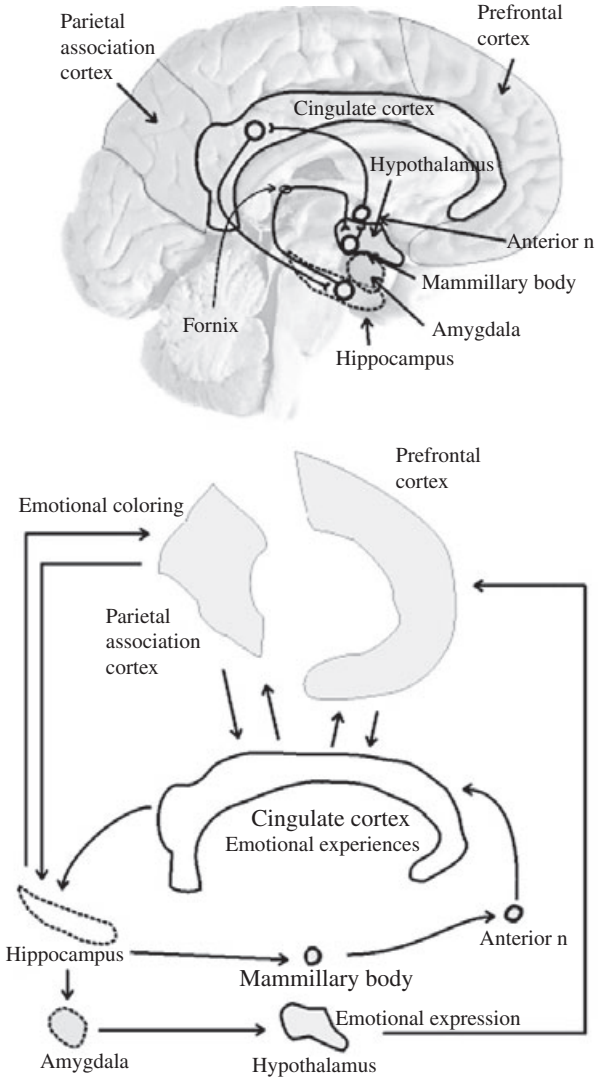

Figure 2 Schematic representation of limbic structures. The top panel provides an anatomic representation while the bottom panel provides dominant functional interrelationships.

competition with potentially stronger alternatives. Patients with lesions to certain zones of the PFC, particularly the ventromedial PFC, have been shown to exhibit profoundly impaired decision making.[19,20] Several studies have demonstrated abnormalities of left PFC function in persons with depression and depressed individuals often experience difficulties responding effectively in situations that are heavily laden with competitive alternative responses.[17,21,22]

PATHOPHYSIOLOGY OF GASTROINTESTINAL PAIN

The discussion above highlights the central role of the limbic system in monitoring and responding to the internal and external environment in a manner that preserves the organism. In this context, emotions can be regarded as nonverbal language allowing us to attend, prioritize and respond to stimuli in our environment. Pain is also a potent nonverbal signal. The central nervous system prioritizes pain transmission amplifying or diminishing pain signals depending upon relevant environmental and internal perceptions.

Ascending pain transmission

Pain perception is an active and plastic process that incorporates sensory, emotional and cognitive experiences. The principal afferent pathways responsible for ascending pain transmission are shown in Fig. 3. Visceral pain is transmitted to the spinal cord and on to the brain by three primary pathways: the spinothalamic, spinoreticular and spinomesencephalic tracts.[23] These divergent pathways process and modulate reflexive, affective and motivational responses to pain. Elegant studies using positron emission tomography (PET) and hypnotic suggestion have helped to discriminate the functioning of these pathways.[24] Hypnotic suggestion does not influence activity of the somatosensory cortex (SSC). Subjects receiving suggestions that a stimulus will be painful have greater activation of the mid-cingulate portion of the ACC than subjects receiving suggestions that the stimulus will be either pleasant or not painful. The mid-cingulate portion of the ACC is an area involved in negative cognitive perceptions such as fear and unpleasantness.

Descending modulation of pain

According to the gate control theory, the brain modulates afferent pain signals by dispersing inhibitory signals to the spinal cord (Fig. 3).[25] Specifically, the pACC, because of its high opioid content and possibly also due to its having been activated by afferent pain signals, sends inhibitory efferent signals directly and indirectly, via the amygdala, to pontomedullary networks.[26] These networks include the periaqueductal grey (PAG), rostral ventral medulla and the raphe nuclei. The inhibitory efferent signals then travel by way of the opioidergic, serotoninergic and noradrenergic systems to the dorsal horn of the spinal cord where they presynaptically inhibit the afferent pain signals. As the ACC and amygdala are implicated in the processing of visceral, attentional and emotional information, the dispersal of inhibitory efferent messages by these structures may be mediated by cognitive, emotional and behavioural factors.

Table 1 The primary connections and functions of human limbic structures

Limbic structure	Primary connection(s)	Functions	Stimulation causes	Lesion results
Hypothalamus	Autonomic nervous system (via hypothalamic –pituitary–endocrine axis); sensory structures in the brain	Govern CNS autonomic function; maintain homeostasis; generate coordinated and sophisticated emotional responses	Emotional responses, incl. anger, fear, curiosity, lethargy	Aberrant autonomic activity; emotional dysregulation
Amygdala	Thalamus; cortex	Process emotions; form emotional memories	Changes in emotion and autonomic function	Impairment in memory for emotionally charged events
Anterior cingulate cortex (ACC)	PFC	Integrate visceral, attentional, and emotional information; regulate affect	Information processing; dispersal of pain-inhibition signals	Profoundly impaired decision-making
Prefrontal cortex (PFC)	ACC	Represent goals; maintain vigilance to goal-directed behaviour; process effect	Increased vigilance; affective processing	Tangential (i.e. non-goal-directed) behaviour

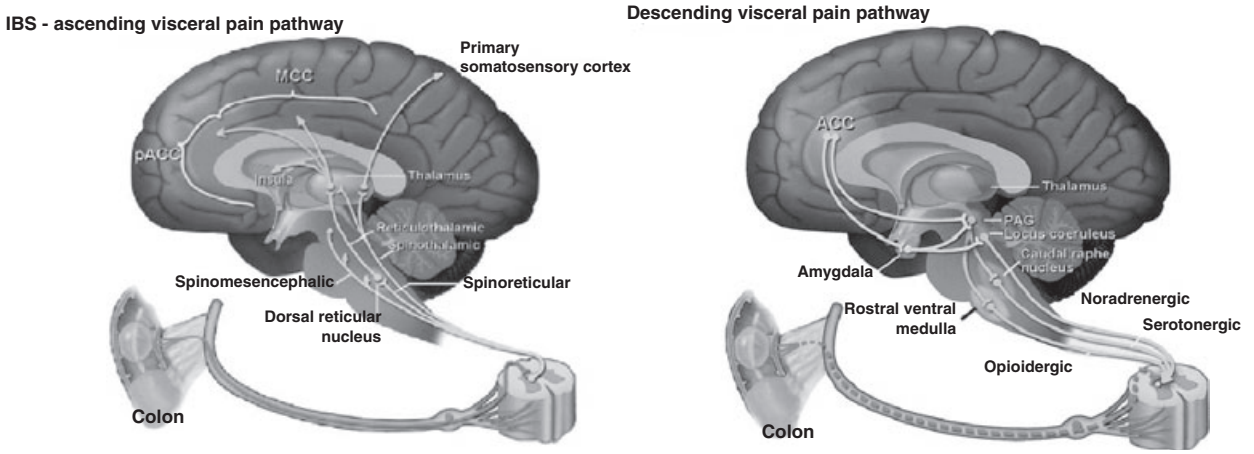

Figure 3 Neuroanatomic pathways mediating visceral pain sensation. The left panel illustrates ascending visceral pain pathways. The spinothalamic tracts provide information that is largely directed to the primary somatosensory cortex and functions to localize and discriminate visceral stimuli. Spinoreticular pathways do not function primarily to localize stimuli but are important in the reflexive, affective and motivational aspects of sensation. Pathways involved in the descending inhibition of visceral pain transmission are shown in the right panel. The anterior cingulate cortex (ACC) exerts influences on mid- and hind-brain structures that project fibres to the dorsal horn of the spinal cord. These opiodergic, serotonergic and noradrenergic pathways regulate the degree to which ascending afferent stimuli are allowed to project to the CNS. From Drossman.[23]

AUTONOMIC FUNCTION IN FGID

The earliest suggestion that alterations in CNS function are associated with FGID came from studies demonstrating alterations in autonomic nervous system (ANS) activity in subsets of patients. Unfortunately, data from these studies have been inconsistent. Various studies have suggested that sympathetic activity may be increased or reduced[27–30] while others have suggested diminished or enhanced parasympathetic tone.[31,32] Some authors have suggested that patients with IBS having constipation or diarrhoea-predominant symptoms have specific patterns of autonomic alterations.[33,34] Unfortunately, no consistent pattern has emerged. Nevertheless, it is commonly observed that a subset of patients with IBS and other FGID have altered autonomic activity associated with flares of their symptoms.[33,35,36]

Central and psychological factors can also be associated with altered ANS activity. Several studies have reported an association between anxiety and depression with altered ANS function in IBS.[32,37]

While other studies have not found such an association, most of these were either methodologically limited in the detection of psychiatric disorders or too poorly powered to allow one to confidently reject an association between psychiatric disorders and autonomic activity.[27,33,38] It is also possible that alterations in ANS function are more strongly linked to acute stress or pain than with psychiatric illness.[28,39,40]

THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS IN FGID

Alterations in the hypothalamic–pituitary–adrenal (HPA) axis are reported in FGID although the area is understudied and observations conflicted. Corticotrophin releasing hormone (CRH) release is reported to be increased in IBS and CRH affects motility and sensitivity in the gut. Further investigation is required to ascertain whether these changes in HPA axis represent a primary event or occur in response to other stressors including digestive symptoms.[41,42] A number of investigators have also reported increased levels of cortisol either at baseline or in response to stress.[34,43,44] but other investigators have not replicated these observations.[38,45]

The HPA axis also affects immune responses and at least one study has demonstrated altered cellular immune function in response to a meal in women with IBS.[45] In patients with postinfectious IBS (PI-IBS), greater psychological distress also characterizes the group of patients with ongoing pain and greater concentration of mucosal inflammatory cells 3 months after the initial enteritis[46] and this may be mediated through altered HPA axis function.

NEUROIMMUNE INTERACTIONS AND PLASTICITY OF THE ENS

The rich neural network of the digestive tract is a unique extension of the ANS capable of generating intrinsic activity independent of extrinsic neural input.[47] The digestive tract also contains the largest component of the immune system in the human body. Complex interrelationships exist between gut associated immune tissue, CNS and ENS (Fig. 4).[48] Additionally, motility disturbances can occur at sites remote from the inflammatory stimulus suggesting that a local insult may actually generate a more diffuse 'field effect'.[47]

Low-grade inflammation or immune activation has been postulated as a basis for alterations in intestinal motility or sensation in at least a subset of patients with IBS.[48,49] A small group of patients with IBS report symptom onset at the time of gastroenteritis (PI-IBS). Prospective studies report persistently abnormal bowel

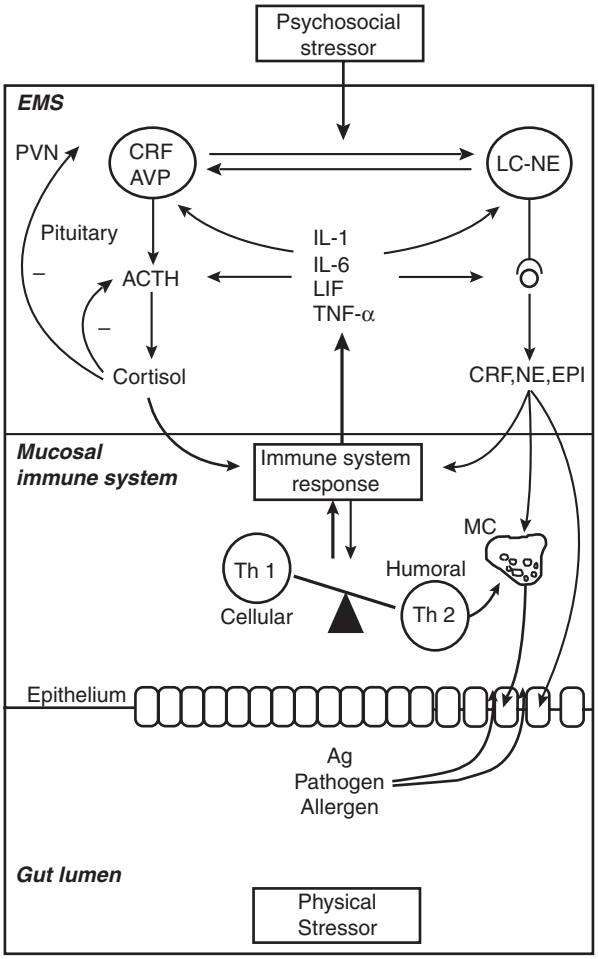

Figure 4 Putative bidirectional brain–gut interactions involved in modulating responsiveness of organism to CNS- and gut-directed stressors. Psychosocial stressors activate stress circuits within the EMS, and the resulting peripheral output in form of neuroendocrine (cortisol), corticotropin-releasing factor (CRF), and autonomic [norepinephrine (NE), epinephrine] responses shifts the mucosal immune system towards a Th2 response (increased mast cells, inducible nitric oxide synthase expression). Autonomic responses can also directly or indirectly modulate gut permeability, thereby changing the access of luminal factors (antigens, bacteria) to the gut immune system. Luminal factors (physical stressors) modulate gut immune function, and immune products from the gut such as cytokines and chemokines can modulate the responsiveness of the EMS. Temporal properties of the stressor and age to the animal at stress exposure are important determinants of type of neuroimmune interaction. ACTH, adrenocorticotropin hormone; AVP, arginine vasopressin peptide; EPI, epinephrine; IL, interleukin; MC, mast cell; LIF, leukemia inhibitory factor; PVN, paraventricular nucleus; Th, T helper; TNF, tumour necrosis factor. From Mayer and Collins.[48]

patterns and symptoms in 9–31% of patients studied.[46,50–53] A case control study using Rome II criteria for IBS reported a incidence of 16.7% 6 months after infection compared with an IBS incidence of 1.9% in healthy controls.[54] The risk of developing PI-IBS is increased 11-fold by an initial diarrhoeal illness lasting longer than 3 weeks or more toxigenic organisms.[52] The likelihood of developing PI-IBS is doubled by the presence of adverse life events at the time of initial illness or hypochondriasis.[46,50]

Patients with PI-IBS have also been shown to have a number of persistent neuroimmune abnormalities. These include increased numbers of intraepithelial T lymphocytes in rectal biopsy specimens, persistent increases in interleukin 1β mRNA expression and increased numbers of mast cells in proximity to mucosal innervation.[55–59] Increased gut permeability has also been reported in a subset of patients with PI-IBS.[56]

FUNCTIONAL NEUROIMAGING IN FGID

While heightened sensitivity to visceral stimuli is postulated as an important pathophysiological mechanism in FGID, mechanisms of visceral hypersensitivity are undetermined. Central modulation of afferent visceral neural pathways attracts increasing evidence and support.[60] Functional neuroimaging is increasingly being used to evaluate central networks involved in processing visceral stimuli in patients with FGID. These studies are cumbersome, technically challenging and interpretation can be highly operator dependent. While these studies call attention to important relationships between CNS and ENS, the findings have not always been consistent. Additionally, it is unclear to what extent functional neuroimaging will advance our understanding of FGID. An understanding of functional neuroimaging studies in patients with FGID is best approached by also understanding functional neuroimaging in healthy subjects in response to pain as well as patients with affective and mood disorders.

Visceral pain and neuroimaging in healthy subjects

In healthy subjects, a common network of cortical and subcortical regions referred to as the 'pain matrix' is consistently activated in response to both visceral and somatic pain. The areas most commonly activated in response to visceral or somatic pain include the mid/anterior insula, subregions of the ACC, PFC, thalamus and pontine regions such as the dorsal pons and PAG.[60]

Several studies have examined brain activations in response to visceral and somatic stimulation (Table 2). Studies examining both somatic and visceral distension have shown fairly consistent patterns of activation although there are differences in representation in the somatosensory cortices.[61–64] In comparing oesophageal balloon distension with midline cutaneous heat, Strigo *et al.*[61] found that heat applied to the midline chest evoked higher activation bilaterally in the anterior insular cortex. Further, cutaneous but not oesophageal pain activated ventrolateral PFC, despite higher affective scores for visceral pain.[61] In addition, visceral pain activated a more anterior locus within ACC. The differences in activation patterns may account for the ability to distinguish visceral and cutaneous pain as well as the differential emotional, autonomic and motor responses associated with these different sensations. Dunckley *et al.*[62] also assessed healthy subject responses to rectal and cutaneous stimuli. This study included visceral and cutaneous stimuli matched for unpleasantness. In general, their findings support the observations of Strigo and colleagues although they differ with respect to ACC response to visceral stimulation.

Limited data exist with respect to regional brain activity in response to gastric distension, but available studies demonstrate activation of the 'pain matrix'.[65–67] There is insufficient evidence to clarify differences resulting from distension of the proximal or distal stomach.

Two studies have evaluated non-painful rectal (visceral) and anal (somatic) distension in healthy subjects.[63,64] Hobday *et al.*[63] found that both rectal and anal distension resulted in similar regions of brain activation although anal distension resulted in activation of the SSC at a greater level and there was no increase in ACC activity. Lotze *et al.*[64] also noted that rectal and anal distension resulted in similar regions of brain activation but that anal stimulation resulted in additional activation of primary sensory and motor cortex, supplementary motor area and left cerebellum.

Neuroimaging abnormalities in affective and mood disorders

Studies of functional neuroimaging in patients with affective and mood disorders are helpful in furthering our understanding of the brain–gut connection. Many of the alterations reported in patients with affective and mood disorders are similar to those seen in patients with FGID. This highlights the close interrelatedness of emotionality and psychosocial distress with gut perception and function. Phan *et al.*[68] recently

Table 2 Changes in regional brain activation between patients with FGID and controls or patients with FGID before and after treatment intervention

Study	Modality	Methods	ACC	PCC	Insula	Brainstem	PFC	Amyg	Thalamus	PPC	SSC
Strigo *et al.*[61] 7 healthy subjects	fMRI	Oesophageal balloon distension	↑ L ACC	nd	↑	na	nd	na	↑	↑	↑
		Midline cutaneous heat	↑ L ACC	nd	↑↑	na	↑↑	na	↑	↑	↑
Dunckley *et al.*[62] 10 healthy subjects	fMRI	Rectal balloon distension	↓↓	↓	↑	↑	↓	na	↑	nd	↑ R side only
		Cutaneous heat to lower back or dorsum of L foot	↓	nd	↑	↑	↑	na	↑	↑	↑
Ladabaum *et al.*[65] 15 healthy subjects	PET	Balloon distension of distal stomach	↑	nd	↑	↑	nd	na	↑	nd	nd
Vandenbergh *et al.*[66] 11 healthy subjects	PET	Balloon distension of proximal stomach	↑	nr	↑	nr	nd		nd	nr	↑
Stephan *et al.*[67] 18 healthy subjects	PET	Balloon distension of proximal stomach	↑	nr	↑	↑	↑	nr	nr	nr	nr
Hobday *et al.*[63] 18 healthy subjects	fMRI	Balloon distension of anal canal	↑	nr	↑	nr	↑	nr	nr	nr	↑
		Balloon distension of rectum	nd	nr	↑	nr	↑	nr	nr	nr	↑
Lotze *et al.*[64] 8 healthy subjects	fMRI	Balloon distension of anal canal	nd	nd	↑	nd	↑	nd	nd	↑	↑
		Balloon distension of rectum	nd	nd	↑	↑	↑	↑	↑	↑	↑↑

↑ Increased rCBF or BOLD signal; ↓ decreased rCBF or BOLD signal.
ACC, anterior cingulate cortex; PFC, prefrontal cortex; Amyg, amygdala; PCC, posterior cingulate cortex; SSC, somatosensory cortex; PPC, posterior parietal cortex; na, not assessed; nr, not reported; nd, no significant difference or change.

reviewed functional neuroimaging studies of human emotions in healthy subjects. These studies vary in task dimensions and type(s) of emotion studied, and are limited by statistical power and sensitivity. Of 11 studies using fear-related stimuli and 15 studies using aversive stimuli, the amygdala was activated in over 60% of studies. Amygdala activation can occur even when the fearful expression is not consciously perceived or even when subjects report a threatening stimulus as non-fearful.[69,70]

No specific brain region has been consistently activated across the spectrum of human emotion although the median PFC is activated in approximately half of all studies using emotional stimuli.[68] Several studies suggest that median PFC activity is particularly increased when subjects are asked to make introspective judgments regarding experiences or feelings.[71–73]

The ACC appears to be activated by tasks involving recalled emotional experiences and with the emotion of sadness. Of the studies reviewed by Phan *et al.*,[68] 50% of studies requiring subjects to recall previous emotional experiences reported ACC activation compared with 31% and 0% of visual and auditory-based emotion studies. Alterations in this region have been found in studies of patients with depression during the resting state,[74,75] and these alterations have been reported to normalize with effective treatment of the depression.[76]

Several studies have assessed regional brain activation in response to placebo. Lieberman *et al.*[77] reported that patients experiencing an effective placebo response demonstrated increased activity in the region of the right ventrolateral PFC and decreased activity in the dorsal ACC. Previous studies have identified the right ventrolateral PFC as an area associated with inhibition in general as well as overcoming negative affect.[78–80]

In a study of depressed patients using PET after receiving fluoxetine or placebo in blinded manner for 6 weeks, Mayberg *et al.*[81] found that responders to either treatment had similar metabolic increases involving the PFC, ACC, posterior cingulate cortex (PCC), premotor, parietal, posterior insular cortices and metabolic decreases involving the subgenual cingulate, parahippocampus and thalamus. Fluoxetine response, however, was also associated with additional subcortical and limbic changes in the brainstem, striatum, anterior insula and hippocampus. These regions are

sources of efferent input to the response-specific regions identified with both agents.

Neuroimaging abnormalities in FGID

Most studies suggest that while patients with IBS may have visceral hypersensitivity, they do not exhibit a generalized hypersensitivity to somatic stimuli.[82–85] Recently, Verne *et al.*[86] demonstrated, however, that compared with healthy subjects, patients with IBS had both visceral and somatic hypersensitivity. Both rectal distension and cutaneous heat activated regions involved in the 'pain matrix' (Table 3). IBS patients showed greater degrees of activation in these regions than controls. While IBS patients did not rate visceral stimulation as more intense than somatic stimulation, they did rate it as more unpleasant. Increased PFC activity (a region associated with affective processing) occurred in the IBS patients and coincided with higher ratings for fear and anxiety given by these patients in response to rectal distension. For controls, visceral stimulation was both more intense and more unpleasant than somatic stimulation. These observations support the hypothesis that visceral and cutaneous hyperalgesia in IBS patients is related to increased afferent processing in pathways ascending to the brain rather than selectively increased activity at higher cortical levels.

Table 3 Changes in regional brain activation between patients with FGID and controls or patients with FGID before and after treatment intervention

Study	Modality	Methods	ACC	Insula	Brainstem	PFC	Amyg	Thalamus	PCC	SSC
Verne *et al.*[86] Ctrls = 9 IBS = 9	fMRI	Rectal distension	↑	↑	na	↑	na	↑	↑	↑
		Cutaneous heat	↑	↑	na	↑	na	↑	↑	↑
Chang *et al.*[87] IBS = 10 IBS + FM = 10	PET	Rectal distension	↑ mACC	nd	nd	nd	nd	nd	nd	nd
		Cutaneous mechanical pressure	↓ mACC*	nd	nd	nd	nd	nd	nd	nd
Mertz *et al.*[88] Ctrls = 16 IBS = 18	fMRI	Rectal distension	↑	na	na	na	na	↑	na	na
Naliboff *et al.*[89] Ctrls = 12 IBS = 12	PET	Anticipated and delivered rectal distension	↓ pACC ↑rostral ACC	na	↓	↓	na	↓	↑	na
Silverman *et al.*[95] Ctrls = 6 IBS = 6	PET	Anticipated rectal distension†	↓ pACC	na	na	↑	na	na	na	na
Berman[91] IBS = 37	PET	Anticipated and delivered rectal distension pre-/post-alosetron	↓pACC	↑	↓ pons	↓vmPFC ↑vlPFC	↓	↑	na	na
Morgan[92] IBS = 19	fMRI	Rectal distension with hi/lo acoustic stress pre-/postamitriptyline	↓pACC	nd	nd	nd	nd	nd	nd	↓
Lackner[90] Ctrls = 6 IBS = 6	PET	Rectal distension pre-/postcognitive therapy	↓pACC	nd	nd	↓	↓	nd	↓	nd

↑ Increased rCBF or BOLD signal; ↓ decreased rCBF or BOLD signal

ACC, anterior cingulate cortex; PFC, prefrontal cortex; Amyg, amygdala; PCC, posterior cingulate cortex; SSC, somatosensory cortex; pACC, perigenual anterior cingulate cortex; sgACC, subgenual anterior cingulate cortex; vmPFC, ventromedial prefrontal cortex; vlPFC, ventrolateral prefrontal cortex; FM, fibromyalgia; na, not assessed or reported; nd, no difference reported between groups.

*Response represents rCBF in IBS compared with IBS + FM groups. In response to cutaneous pressure, the IBS + FM group demonstrated greater mACC activity as well as increased activity in the thalamus.

†No differences in rCBF were seen between IBS and ctrl groups for painful and non-painful distensions. For brevity, this condition is omitted from the table.

Chang *et al.*[87] studied responses to visceral and somatic pain in patients with either IBS or IBS and fibromyalgia. IBS patients regarded visceral stimulation as more unpleasant than somatic stimulation while patients with IBS and fibromyalgia rated visceral and somatic stimuli as equally unpleasant. This was paralleled by activity changes in the middle subregion of the ACC. There was a greater regional cerebral blood flow (rCBF) increase in the ACC in response to visceral stimuli in patients with IBS and to somatic stimuli in patients with both IBS and fibromyalgia (Table 3). This highlights the important observation that CNS responses to visceral and somatic stimuli do not appear condition-specific but simply reflect central mechanisms of afferent processing.

Mertz *et al.*[88] demonstrated that rectal distension in both controls and patients with IBS activated similar brain regions. While rectal distension led to greater ACC activation in patients with IBS than in controls, the degree of activation did not correlate with reported pain severity. These data suggested a qualitatively normal but quantitatively enhanced pattern of CNS activation in patients with IBS.

Naliboff *et al.*[89] used PET to evaluate regional brain activity in response to real *vs* simulated rectal distension in healthy subjects and patients with IBS.Figure 5 shows between-groups comparisons of PET scan images from controls and patients with IBS in response to both actual and anticipated rectal distension. Compared with controls, patients with IBS had increased rCBF in the right PFC, ACC and PCC and decreased activity in the pACC, temporal lobe and brainstem.

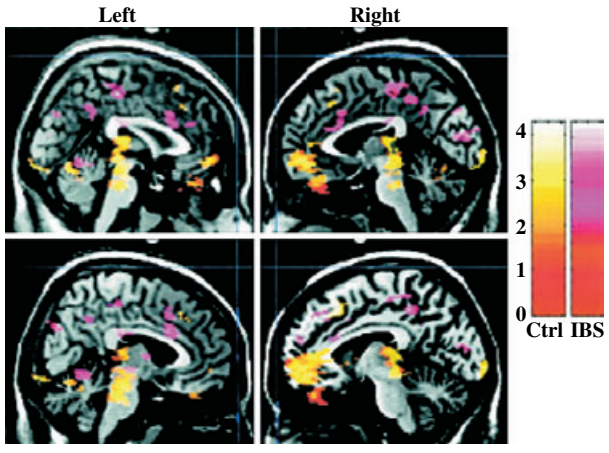

Figure 5 Summary of control (yellow scale) and IBS (pink scale) responses along the medial surface of the anterior cingulate cortex for the comparison of stimulation and anticipation with the baseline before and after conditioning. Two slices are shown from the left and right hemisphere to a depth of 2 mm (top) and 6 mm (bottom). From Naliboff *et al.*[89]

These responses occurred even when rectal distension was anticipated but not delivered suggesting that IBS patients may have reduced activation of neural circuits associated with antinocioceptive responses to aversive stimuli (ACC) and preferential activation of regions involved in processing negatively charged emotional information (PFC).

Silverman *et al.* also found that patients with IBS responded to actual or anticipated rectal distension with significant activation of the PFC. While healthy subjects displayed ACC activation in response to administered or anticipated pain, no such pattern was seen in the IBS patients. The authors concluded that painful rectal distension in healthy subjects was associated with ACC activity but patients with IBS displayed an aberrant response in response to both actual and anticipated visceral pain.

The above studies demonstrate that in patients with IBS, CNS responses to unpleasant or painful visceral stimuli produce patterns of CNS activity that are qualitatively similar to controls. Differences exist between patients and controls with respect to anticipated stimulation and the correlation between reported experience and ACC activation. While more detailed study is needed in this area, the reviewed studies suggest that an important determinant pain behaviour in patients with IBS may be attentional rather than an abnormality of afferent transmission.

Influence of behavioural and pharmacological therapies on neuroimaging in FGID

Lackner *et al.*[90] reported a series of six individuals with IBS and six controls. Patients with IBS were treated with a 10-week course of cognitive therapy. Treatment was associated with a significant reduction in anxiety and digestive symptoms. PET scans showed reduced activity in the region of the left amygdala and right ACC following therapy (Table 3 and Fig. 6).

Berman *et al.*[91] reported that patients with IBS treated with alosetron compared with placebo-treated controls had reduced rCBF as measured by PET in the ventromedial PFC, infragenual cingulate, hypothalamus, ventral striatum and amygdala. Symptom improvement correlated with decreased rCBF in the amygdala, ventral striatum and dorsal pons. The alosetron-associated reduction in rCBF was greatest at rest and less pronounced during rectal or sigmoid distension. The same group published a second study of the effects of alosetron on regional brain activation and symptom responses to rectal distension after a 3-week, placebo-controlled trial of alosetron in male and female patients with non-constipation IBS.[91]

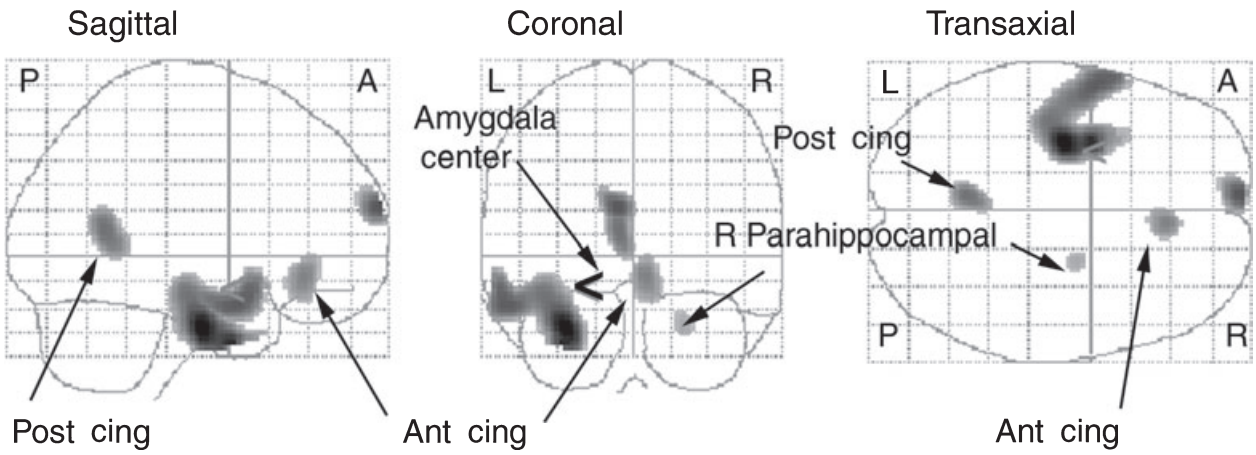

Figure 6 Brain regions showing reduced neural activity after cognitive therapy. The most pronounced reductions occurred in the region of the left amygdala and right anterior cingulated cortex. From Lackner *et al.*[90]

Treatment with alosetron but not placebo was associated with a decrease in symptom ratings and reductions in emotional stimulus ratings. Alosetron treatment was associated with reduced rCBF in bilateral frontotemporal and various limbic structures, including amygdala. It is unclear whether or not the observed effects were related to central or peripheral actions of the drug.

Finally, Morgan *et al.*[92] showed similar effects on cingulate activation after treatment with the a tricyclic antidepressant amitriptyline. Females with IBS were randomized to amitriptyline 50 mg daily or placebo in a crossover fashion. Rectal balloon distension was performed under both stressful and non-stressful conditions. Treatment with amitriptyline resulted in decreased pain-related activations of the pACC and left posterior parietal cortex, but only during stress. Amitriptyline did not significantly reduce ratings of pain intensity nor did it influence activity in the insular cortex (where visceral sensation is represented). These data suggest that low dose tricyclic antidepressants (TCA) may improve symptoms in patients with IBS by diminishing the inhibitory effects of stress on ACC function.

These reports suggest that symptom improvement in IBS with behavioural therapies, serotonergic agents and antidepressants is associated with changes in brain activations in areas associated with the affective and cognitive processing of pain. Whether the observed responses to treatment reflect primary effects or epiphenomenon is undetermined.

Overview of neuroimaging in IBS

Studies discussed above that evaluated patients with IBS either compared with controls or pre- and post-therapeutic intervention are summarized in Table 3. Overall, there are a small number of studies containing small sample sizes. While discrepancies exist, most studies demonstrate heightened activity in regions previously noted to be involved with visceral or somatic pain.[93] These areas include pACC, mACC, PFC, insula, SSC and thalamus. The three studies evaluating treatment interventions have all shown decreased activity in the pACC after treatment but effects on brain activity in other regions have not been as consistently reported. Whether these interventions specifically target brain regions identified is unknown at present.

While it seems that difference do exist between patients with IBS and healthy subjects with respect to regional brain activation, functional neuroimaging is not yet developed enough to provide more specific information or to clarify these reported differences and their relationship to stress, pain and emotion.[94] These studies suffer from a variety of methodological limitations that are summarized in Table 4. The true value of functional neuroimaging will only become apparent when these issues have been successfully addressed.

CONCLUDING COMMENTS

Understanding the neural regulation of gut function and sensation makes it easier to understand the interrelatedness of emotionality, symptom-attentive behaviour or hypervigilance, gut function and pain. The gut and the brain are highly integrated and communicate in a bi-directional fashion largely through the ANS and HPA axis. Within the CNS, the locus of gut control is chiefly within the limbic system, a region of the mammalian brain responsible

Table 4 Methodological limitations of current functional neuroimaging studies in patients with FGID. Adapted from Drossman[94]

Activations often involve neural circuitry of several interacting regions which make it difficult to target single sites
Potential imaging differences between PET and fMRI
Gender differences
Confounding effects on the registration of images to rectal distension with anticipation of that event
Confounding central influences, such as placebo effects
Clinical heterogeneity among patients with regard to diagnosis and severity of the disorders
Methodological issues in technique, lack of instrument and protocol standardisation, low 'signal to noise' ratios, and limitations in measuring functionally heterogeneous regions of the cingulate and other brain regions.

for both the internal and external homeostasis of the organism. The limbic system also plays a central role in emotionality, which is a nonverbal system that facilitates survival and threat avoidance, social interaction and learning. The generation of emotion and associated physiological changes are the work of the limbic system and, from a neuroanatomic perspective, the 'mind–body interaction' may largely arise in this region. Finally, the limbic system is also involved in the 'top–down' modulation of visceral pain transmission as well as visceral perception.

A better understanding of the interactions of the CNS, ENS and enteric immune system will significantly improve our understanding of 'functional' disorders and allow for a more pathophysiological definition of categories of patients currently lumped under the broad umbrella of FGID.

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