The balancing act: endogenous modulation of pain in functional gastrointestinal disorders

Clive H Wilder-Smith

ABSTRACT
Functional gastrointestinal disorders (FGIDs) are characterised by visceral pain or discomfort with an unknown cause. There is increasing evidence for abnormal processing of sensory input in FGIDs. Modulation of sensory input occurs at all levels of the nervous system, with a dynamic balance between facilitation and inhibition and close integration with the body’s wider homoeostatic control. Cognitive, emotional, autonomic and spinal reflex pathways effectively orchestrate supraspinal and spinal pain modulation, as demonstrated in neurophysiological and brain imaging studies. Endogenous pain modulation has been studied in visceral pain conditions and abnormal regulation has been shown in irritable bowel syndrome (IBS) and functional dyspepsia, as well as other chronic pain syndromes. A majority of patients with IBS have diminished pain inhibition or even pain facilitation compared with healthy controls. Brain imaging during specific activation of endogenous pain modulation demonstrates a fairly consistent functional hub of mainly frontal, limbic and brainstem modulatory regions in healthy humans. Patients with IBS have a different pattern of activation and a correlation between the imaging and sensory changes. Because the modulatory balance of inhibition and facilitation appears to be distributed within the same functional network, future imaging studies of modulation mechanisms should include conditions allowing quantification of inhibitory and facilitatory components. An altered modulatory balance may well be a unifying pathophysiological mechanism in FGID as it can be driven by both top-down (ie, CNS pathology) and bottom-up (ie, peripheral immune activation) influences, but further validation in diverse FGID groups over time is required. Therapeutic manipulation of the modulatory system is possible by both pharmacological and non-pharmacological means.

INTRODUCTION
Visceral pain is one of the most frequent reasons for medical consultation and is an integral part of the most common gastrointestinal syndromes—the functional gastrointestinal disorders (FGIDs) such as irritable bowel syndrome (IBS) and functional dyspepsia (FD). Recent evidence is transforming our concepts regarding the pathogenesis of visceral pain in FGIDs as a prominent number of affected individuals can now been shown to have either cognitive, behavioural or sensory dysfunction, or subclinical signs of immune activation, all with very similar clinical symptoms.1 Pain represents an integrated response of multiple body systems which affect homoeostatic control functions, such as autonomic nervous and immune regulation.1 Chronic pain is often accompanied by a lowered pain threshold (allodynia) and increased pain to a stimulus (hyperalgiesia).3 This sensitisation may be driven by peripheral, spinal or central nervous system changes. Recent data suggest that an individual’s pain response is dependent on the unique dynamic balance between pain inhibition and facilitation, providing at least a partial explanation for the widely differing pain responses.4 5 The balance between pain inhibition and facilitation is governed by a modulatory network of brain and brainstem regions closely linked to spinal pathways.5–6 Pain modulation has been shown to be abnormal in several chronic pain disorders (see box 1). The ability to favourably influence endogenous pain modulation (EPM), pharmacologically as well as cognitively, emphasises the clinical importance of these mechanisms. This paper discusses the role of the body’s pain regulatory mechanisms in FGID. These mechanisms will collectively be referred to as EPM (see box 2).

BACKGROUND
Physiology of EPM
Endogenous modulation of pain can be defined as the body’s adaptation of incoming nociceptive information to momentary as well as long-term circumstances and needs. This definition closely parallels the definition of homoeostasis proposed by William Cannon in the early 1900s: the property of a living system to regulate its internal environment to maintain a stable constant condition.3 5 Pain modulation is a dynamic process balancing inhibition and facilitation and is intricately connected to other homoeostatic systems (figure 1).2 3 6 7 19

Modulation can occur at all levels of the sensory nervous system—that is, the peripheral, spinal and supraspinal levels—as well as via the autonomic nervous system and is dependent on the context of the injury as well as endogenous factors such as the psychological and genetic background (figure 1). This review will concentrate on the central so-called descending modulation of pain, but a brief summary of modulation at the more peripheral levels is included for better understanding of the integration between all levels of pain processing (figure 2).
Recent advances in clinical practice

**Box 1 Conditions in which endogenous pain modulation has been shown to be dysfunctional**

- Irritable bowel syndrome
- Fibromyalgia
- Functional dyspepsia
- Chronic pancreatitis
- Temporomandibular joint dysfunction
- Increased postoperative pain/requirements for analgesia
- Migraine
- Tension-type headache
- Osteoarthritis
- Rheumatoid arthritis
- Chronic trapezius myalgia
- Neuropathic pain
- Chronic widespread pain
- Pain catastrophising

**Peripheral pain modulation**

Injury or inflammation can lead to persistent peripheral input and sensitisation. In IBS there is mounting evidence of sensitisation and of chronic low-grade intestinal immune activation probably associated with increased intestinal permeability. Upon tissue insult, pro-algesic and pro-inflammatory mediators are released by immune, neuronal, endothelial and epithelial cells. This aghesic process is balanced by endogenous analgesic mechanisms including the release of endogenous opioid peptides released in the immediate vicinity of sensory neurons and acting on mu-(MOR), delta- (DOR) and kappa- (KOR) opioid receptors have a distinct local analgesic and anti-inflammatory effect. The analgesic effect is dependent on the presence of inflammatory cells and hence inflammation.

**Supraspinal (descending) modulation of pain**

The function of the supraspinal pain control pathways is to either amplify or to subordinate noxious or potentially noxious stimuli in coordination with the individual’s homeostatic needs. Control of the brain over spinal input is both inhibitory and facilitatory and, importantly, the same brain centres can exert both inhibitory and facilitatory influences. The majority of research on descending pain modulation has concentrated on inhibition, which has led to an ambiguous interpretation of brain imaging data in visceral pain. Regulation of the dynamic balance between inhibition and facilitation occurs within the brainstem rostroventral medulla (RVM) - periaqueductal grey (PAG) axis and in connected brainstem and higher cortical centres. The brainstem modulation may not be restricted to pain but appears to extend to a wide range of homeostatic mechanisms. The balance of modulation depends on the type of activated afferent nerve fibres, the duration, the type and the background state or context of the injury. Chronic and intense noxious stimulation involving C-nerve fibres more commonly leads to sensitisation and activates modulatory mechanisms more extensively than short-lasting input. This distinction may explain some of the divergent results in sensory studies of IBS and other chronic pain states.

**Box 2 What is endogenous pain modulation and what is its relevance in gastroenterology?**

- All painful input is modulated at the levels of the peripheral nerve, the spinal and supraspinal (brainstem and brain) nervous system. These levels are intricately connected and modulate other homeostatic mechanisms as well as pain.
- Modulation is a dynamic balance between inhibition and facilitation, which is influenced by bottom-up (ie, spinal and peripheral) as well as top-down (ie, central nervous system) factors. This balance is highly individual and appears to correlate with different clinical measures of pain sensitivity.
- Pain modulation is abnormal in irritable bowel syndrome as well as in other chronic pain conditions, with a decrease in the inhibition seen in health or a facilitation. This may be driven by peripheral inflammation as well as by psychological changes.
- Endogenous pain modulation is strongly influenced by cognitive, analgesic and anti-inflammatory measures and may explain some of their therapeutic effectiveness.

**Spinal pain modulation**

Extensive adaptation of peripheral afferent sensory input occurs at the spinal level, with a dynamic balance of inhibition and facilitation conferred by local interneurons and by multiple pathways originating supraspinally. Pro-inflammatory cytokines, chemokines, biogenic amines, bradykinins, prostaglandins, substance P, calcitonin-G-related peptide and several neurotrophins are among the facilitatory mediators. Endo-oidopioids, anti-inflammatory cytokines and endocannabinoids tip the balance in favour of inhibition. Depending on the subtype of receptor activated, serotonin, dopamine and noradrenaline can have either excitatory or inhibitory function. Feedforward and feedback control of input is effected via spinal-supraspinal-spinal loops. Nociceptive input is conveyed from the dorsal horn to subcortical nuclei and then onwards to a hub of brain processing regions (figure 3).
pathways including the so-called diffuse noxious inhibitory controls (DNIC).\textsuperscript{12, 44, 45} Isolated perceptual modulation of pain at a cortical level or by brainstem-spinal loops is unlikely.\textsuperscript{41–43} Descending control over spinal dorsal horn neuronal activity is through noradrenergic, opioderergic, serotoninergic, dopaminergic and cannabi-noid pathways which themselves can be either inhibitory or facilitatory depending on the receptor subtype activation (figure 4).\textsuperscript{6, 13, 30, 37, 46–58}

**Modulation by the autonomic nervous system**

Sensory processing from the viscera differs from the superficial organs in the extensive primary involvement of the autonomic nervous system (see recent reviews\textsuperscript{50–61}). Parasympathetic vagal afferents contain large numbers of sensory fibres relaying information to brainstem regions and then onwards to forebrain centres.\textsuperscript{62, 63} The overlap of these areas with those responsible for bodily homeostasis and pain-related responses, such as illness behaviour, autonomic, emotional, motor and immune reactions, emphasises extensive visceral input convergence and integration.\textsuperscript{62, 64} Vagal stimulation may attenuate pain both centrally and peripherally and has an anti-inflammatory effect.\textsuperscript{65}

The sympathetic nervous system appears to exert little influence on pain in physiological conditions, but possibly plays a role in neuropathic pain states.\textsuperscript{48} An important efferent function of the sympathetic nervous system is the control of immune activation via the locus coeruleus, influencing inflammatory activity and the immune responses central to most forms of chronic pain.

**ENDOGENOUS PAIN MODULATION (EPM) IN FGIDS**

The dynamic balance between pro- and anti-nociception and the integration with other bodily control mechanisms is clearly established in health. Changes in this equilibrium may well play an important role in chronic visceral pain syndromes, with a shift towards sensitisation and pain facilitation. In the following sections, evidence of changes in pain modulation in IBS as well as early data for FD is summarised. FGIDs are associated with several factors which potentially shift the balance of pain modulation such as stress, anxiety, chronic inflammation and hypervigilance as well as other pain comorbidities.\textsuperscript{1, 66–69} Because of the extensive integration of the modulatory pathways, both bottom-up (eg, chronic mucosal immune activation) as well as top-down (eg, cognitive-limbic dysfunction) influences could drive the disequilibrium.

**Sensory testing shows abnormal EPM in FGIDs**

Evidence for altered endogenous sensory modulation in FGIDs exists at several levels. Quantitative sensory testing has confirmed visceral and— depending on the stimulation procedure—somatic hypersensitivity in a majority of patients with IBS.\textsuperscript{70–75} This suggests sensitisation, but is not proof of abnormal modulation. Several test procedures have been developed specifically to
assess EPM (see box 3). The best characterised model is termed DNIC, heterotopic stimulation or heterotopic noxious conditioning stimulation, where a primary painful stimulation is applied alone and then simultaneously with a second distant conditioning stimulation which normally reduces the pain intensity of the primary stimulation (figure 5). DNIC mechanisms have been extensively validated both in health and in disease in animals and in humans with a flexion reflex (RII reflex) or the closely correlated changes in pain ratings.76–84 They are classically postulated to engage spino-bulbo-spinal pain modulatory loops, but recent brain imaging studies have shown considerable involvement also of supraspinal and cortical regions.44 45 85 It should be pointed out that heterotopic stimulation does not separately identify the magnitude of inhibition and facilitation, but quantifies the summation of both effects. A further stepwise water immersion paradigm has also been developed.86 Using these techniques, either a decreased pain inhibition or a facilitation compared to controls has been demonstrated in a majority of patients with IBS from a variety of ethnicities (figure 6), and there was a good correlation between the magnitudes of abnormal pain modulation and of changes in pain sensitivity.44 45 75 87 90 The presence of both abnormal visceral and somatic pain modulation as well as sensitisation in IBS indicates a generalised rather than a specifically visceral sensory disorder. This pain modulation is not sufficiently explained by distraction or attentional effects, although emotional and cognitive effects feed into the same general modulatory network.44 91 92 In healthy controls, heterotopic stimulation generally achieves a pain inhibition of 15–35%, with some racial differences between Asians, Black Africans and Caucasians.76 90 93 Over the past few years work by our group has demonstrated abnormal modulation by heterotopic stimulation in 70–85% of patients with IBS, with facilitation rather than inhibition occurring in approximately 50% and weaker than normal inhibition in the majority of the remaining patients.44 45 75 More recently, abnormal EPM has also been demonstrated in patients with FD using a novel and reproducible heterotopic stimulation model with capsaicin-induced gastric pain and simultaneous thermal foot pain.94 In healthy controls the gastric pain was reduced by a highly significant 65% by heterotopic foot stimulation compared with an insignificant reduction in patients with FD.94 Furthermore, the magnitude of abnormal modulation in patients with FD correlated with their clinical symptom intensity.94 The data in FD needs confirmation in larger trials and in subsets of patients with FD. These simple psychophysical techniques demonstrate abnormal modulation in most but not all patients with IBS and FD, and further validation in large diverse groups of patients with FGIDs in longitudinal studies is advised. Integration of the assessment of EPM with studies of other potential disease mechanisms such as immune activation, autonomic...
Figure 5 Model for testing endogenous pain modulation using heterotopic stimulation. Heterotopic stimulation denotes modulation of a primary pain stimulus by a second distant (heterotopically applied) painful stimulus. The change in primary pain stimulus intensity is the outcome measure. The graph shows typical results for pain intensity of primary pain alone (red bar), pain intensity of primary pain together with heterotopic stimulus (yellow bar) and the pain intensity decrease due to the heterotopic stimulus (green bar).

Box 3 Methods of assessing endogenous pain modulation

- Sensory testing using heterotopic stimulation—that is, two simultaneous and distant painful stimulations (eg, rectal distension and thermal hand stimulation).
- Stepwise limb immersion and withdrawal from thermal water stimulus.
- Manipulation of pain processing by cognitive or emotional input—for example, by variation of expectation (placebo/nocebo), suggestion, distraction, stress or anxiety.
- Brain imaging with fMRI or PET during modulation of pain.
- Brain and spinal electrical activity changes during modulation of pain—for example, cerebral evoked potentials.

Abnormal EPM in FGID by brain imaging

fMRI and positron emission tomography studies have been pivotal in elucidating the brain areas and networks activated during pain, discomfort and cognition-related tasks in health and FGID. However, the experimental context and study design require a critical interpretation regarding applicability to clinical situations. An in-depth review of these imaging studies is beyond the scope of this specialised paper and the reader is referred to excellent recent publications. Abnormal pain modulation has also been shown with these tests in fibromyalgia, which often overlaps with FGID, and in other chronic pain syndromes.

Abnormal EPM in FGID by brain imaging

fMRI and positron emission tomography studies have been pivotal in elucidating the brain areas and networks activated during pain, discomfort and cognition-related tasks in health and FGID. However, the experimental context and study design require a critical interpretation regarding applicability to clinical situations. An in-depth review of these imaging studies is beyond the scope of this specialised paper and the reader is referred to excellent recent publications. Abnormal pain modulation has also been shown with these tests in fibromyalgia, which often overlaps with FGID, and in other chronic pain syndromes.
modulatory dysfunction in IBS, corresponding to attentional and cognitive changes such as hyper-vigilance and increased symptom-directed anxiety, is visible in the abnormal prefrontal cortex activation patterns. The diminished prefrontal activation often demonstrated in IBS is also associated with negative emotions and increased pain.

The success of hypnosis in IBS may reflect a modulatory effect with increased prefrontal activation feeding into the downstream modulatory areas, resulting in distancing from the emotional impact of pain and in pain reduction.

Brain activation differences during a sensory stimulus between patients with IBS and controls are frequently ascribed to abnormal endogenous sensory inhibition. While associations are possible in these studies with generally smaller numbers of subjects, certain caveats need to be mentioned as the associations between imaging and function are unlikely to be linear for several reasons: the complex relationship between neuronal activation, perception and BOLD fMRI signal change; the involvement of the same brain centres in both inhibitory and facilitatory actions; and a shifting modulatory balance with chronic input. Furthermore, many of the classic modulatory brain centres are also extensively involved in regulation of non-nociceptive functions. To address these issues, several studies have included paradigms actively engaging quantifiable pain modulation during imaging. These paradigms include attentional and emotional modulation, placebo and nocebo procedures and the above-described heterotopic stimulation. All of these procedures significantly and quantifiably alter pain intensity but, nonetheless, they bear the limitations inherent in the application of acute experimental procedures to a chronic disease setting. We will consider the relevant studies relating to IBS below.

Brain imaging during activation of EPM by heterotopic stimulation in IBS

Heterotopic stimulation has demonstrated abnormal pain modulation in IBS and, consistent with this, concurrent brain imaging has shown aberrant brain activation in areas associated with the cognitive and emotional modulation of pain (figures 8 and 9). The processing seen in the classic modulatory regions during effective pain inhibition in controls contrasts with the increased activations in the so-called ‘fear and threat’ network in IBS during pain facilitation or decreased

modulatory dysfunction in IBS, corresponding to attentional and cognitive changes such as hyper-vigilance and increased symptom-directed anxiety, is visible in the abnormal prefrontal cortex activation patterns. The diminished prefrontal activation often demonstrated in IBS is also associated with negative emotions and increased pain.

The success of hypnosis in IBS may reflect a modulatory effect with increased prefrontal activation feeding into the downstream modulatory areas, resulting in distancing from the emotional impact of pain and in pain reduction. On the other hand, there is also evidence in imaging studies of increased intestinal (peripheral) sensory input due to sensitisation or subcortical facilitation in IBS. Thus, with identical rectal stimulus intensity, brain activation in the early pain processing areas was greater in IBS than in controls whereas, in subjective rating-matched stimulation, there were only minor activation differences in these areas between subject groups. Several recent interesting studies have examined the linkage between the main pain processing centres in IBS using connectivity analysis. However, owing to the absence of adequate control groups, they can only provide indirect evidence of any disease-related changes in modulation and will not be considered here.
inhibition. Moreover, the diminished endogenous pain inhibition in patients with IBS correlated with the activation changes in the key pain processing areas and also with the presence of somatic and visceral hyperalgesia.\textsuperscript{44, 45} Analysis of functional brain connections during pain modulation induced by heterotopic stimulation showed top-down control of cortical brain areas over key brainstem modulatory areas in healthy controls but a reversed bottom-up direction of control in patients with IBS.\textsuperscript{121} The predominantly quantitative rather than qualitative activation differences in IBS imaging studies may well be due to a shifted gain within the modulatory balance in these central control areas, as has been demonstrated in various forms of chronic pain in animals by Vanegas and Schaible.\textsuperscript{19} In summary, current pain modulation brain imaging studies support the presence of abnormal EPM in IBS. We are not aware of any brain imaging studies during explicit modulation of pain in FD.

**Brain imaging during psychological modulation of pain and IBS**

The individual experience of pain is powerfully influenced by cognitive and emotional mechanisms such as the expectation and desire of pain relief (placebo), the expectation of pain (nocebo), memory, reward and mood.\textsuperscript{124, 125} Expectation may explain up to 50% of the variation in pain ratings.\textsuperscript{125} Placebo and nocebo effects appear to represent a continuous spectrum of responses rather than qualitatively different mechanisms.\textsuperscript{126} This balance between hypo- and hyperalgesia, or inhibition and facilitation, is predominantly regulated by endogenous opioid and cholecystokinin systems.\textsuperscript{127} Cholecystokinin is implicated in hyperalgesia mediated in the PAG, counterbalancing opioid-induced analgesia, and also in the pathogenesis of IBS.\textsuperscript{128–132}

Brain imaging studies with placebo in healthy individuals have shown a correlation between the degree of expected pain relief and brain activation in main modulatory (especially opioidergic) areas.\textsuperscript{14, 50, 52, 101, 133–136} However, dopaminergic reward pathways in the basal ganglia also account for approximately 25% of the variance of placebo responses.\textsuperscript{34} Placebo analgesia manipulates activity in cortical and subcortical regions key to the cognitive and emotional modulation of pain. Importantly, the anticipation of pain and of nocebo-induced hyperalgesia activated very similar brain regions.\textsuperscript{15, 16, 136–140} The overlap in brain areas activated during cognitively-induced pain inhibition and pain enhancement again suggests a modulation executed within an overlapping functional network.

Comparatively few brain imaging data have been published examining cognitive and emotional effects on pain in FGID. However, these modulatory mechanisms are of particular relevance in FGID, where memory of abuse, somatisation, negative mood, symptom-related anxiety, selective attention and hypervigilance are implicated in pathogenesis and where expectation and placebo...
responses are considered elevated. In patients with IBS the history of abuse was associated with activation differences compared with controls in distinct subregions of the cingulate cortex during rectal distension. In a separate study, increased anxiety during expectation of a rectal distension in patients with IBS correlated with an absence of deactivation in arousal network regions, especially the dorsal brainstem. Therefore, although associations between psychological processes, gastrointestinal sensory function and symptoms have been shown in patients with FGID during functional brain imaging, most studies have been performed in uncontrolled settings in IBS. Rectal placebo with the suggestion of enhanced analgesia in IBS reduced both rectal distension pain ratings and brain activations in divisions of the insula and ACC compared with rectal distension alone. Functional connectivity analysis yielded differences in the direction of influence within modulatory areas with placebo. Further controlled studies are needed to better characterise the psychological modulation of pain in FGID and visceral pain in general.

**Therapeutic implications of EPM in FGID**

The descending pain modulatory pathways can be manipulated with a wide range of medications including opioidergic, serotonergic, noradrenergic, dopaminergic and non-steroidal anti-inflammatory drugs. Given the close integration of cognitive, emotional and modulatory processes, it would be expected that behavioural and cognitive treatments exert their principal effects via the modulatory pathways. Indeed, imaging and psychophysical data provide corresponding supportive evidence for placebo and nocebo studies, and data emerging from trials of hypnosis, cognitive behavioural therapy, mindfulness and dynamic psychotherapy indicate that their potential effectiveness in the treatment of FGID may be via the modulatory networks. There are therefore considerable pharmacological and non-pharmacological therapeutic possibilities of manipulating EPM that deserve further exploration with high-quality studies.

**Conclusions and future directions**

There is increasing evidence for abnormal EPM in IBS and FGID, with a shift in balance from inhibition towards facilitation. EPM may be part of the body’s integrated and dynamic homeostatic response and probably explains some of the related changes in other regulatory systems in FGID such as autonomic function, immune, cognitive and gastrointestinal motility changes. Both top-down (ie, CNS dysfunction) and bottom-up (ie, spinal and peripheral immune activation) could reset EPM (figure 10). Undoubtedly, the very loose phenotypical definition of FGID encompasses different subgroups of pathologies, however disordered function of a central regulator of homeostatic functions would go far in explaining some of the divergent manifestations. As Sherrington suggested in 1900: ‘Pain is a curiously imperative occurrence that co-opts descending bulbospinal neurons to make necessary adjustments to sensory, autonomic and motor functions’.

Brain imaging is increasingly defining the predominant structures involved in the modulation of pain. The pathways and centres governing the balance between pain inhibition and facilitation largely overlap. Future imaging studies should therefore include conditions allowing quantification of inhibitory and facilitatory components. Comparisons between healthy controls and patients with FGID incorporating the assessment of peripheral, spinal and supraspinal modulation during placebo and nocebo manipulation are necessary to further define the aberrant pain modulation in FGID.

**Competing interests** None.

**Provenance and peer review** Commissioned; externally peer reviewed.

**References**


Recent advances in clinical practice


Recent advances in clinical practice


Gut 2011;60:1589—1599. doi:10.1136/gutjnl-2011-300253
Recent advances in clinical practice

The balancing act: endogenous modulation of pain in functional gastrointestinal disorders
Clive H Wilder-Smith

_Gut_ 2011 60: 1589-1599 originally published online July 18, 2011
doi: 10.1136/gutjnl-2011-300253

Updated information and services can be found at:
http://gut.bmj.com/content/60/11/1589

References
This article cites 150 articles, 17 of which you can access for free at:
http://gut.bmj.com/content/60/11/1589#ref-list-1

Topic Collections
Articles on similar topics can be found in the following collections
- **Gut Education** (56)
- **GUT Recent advances in clinical practice** (106)
- **Dyspepsia** (297)
- **Irritable bowel syndrome** (327)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/