Central Nervous System Processing of Human Visceral Pain in Health and Disease

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To understand the pathophysiology of anomalous pain in functional gastrointestinal disorders, we must increase our understanding of how the central nervous system processes visceral pain. Over the past decade, novel application of functional brain imaging and electrophysiological techniques has given us the opportunity to study these processes in humans, and this review summarizes the current body of knowledge.

Pain is a subjective, psychological experience that teaches us to avoid potentially harmful events, ensures that we protect damaged tissue while it heals, and is essential to promote our longevity. However, just as disorders of our other senses, such as sight, affect our ability to function optimally, aberrant pain processing can lead to severe, debilitating conditions that pervade all aspects of life.

The experience of pain most commonly begins with a noxious stimulus that is transmitted along nociceptive pathways to the brain. The brain receives this signal and integrates sensory, cognitive, and emotional information to produce an appropriate response. Unfortunately, pain commonly occurs in the absence of apparent tissue damage and/or noxious stimuli, as is found in functional pain syndromes such as fibromyalgia and irritable bowel syndrome. These conditions are among the most common seen by clinicians, yet few successful treatments exist.

Our ability to understand the etiology of pain in both organic and functional pain syndromes relies on unraveling the specific contributions and connectivity of the many brain regions involved in pain processing. Our knowledge in this area has been greatly enhanced by functional brain imaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). These techniques have allowed researchers to identify the anatomy of the cortical pain matrix, and elegantly designed paradigms have begun to reveal the functional relevance of discrete cortical regions to different aspects of the pain experience (for reviews, see Refs. 13 and 17).

The majority of research has concentrated on superficial pain such as that evoked by thermal stimulation of the skin. More recently, however, functional brain imaging techniques have also been used to study the visceral cortical pain matrix. Visceral pain has several unique qualities and characteristics that distinguish it from somatic pain. It is characterized by poor localization, tonic increases in muscle tone, and a propensity to evoke strong autonomic responses such as changes in heart rate and blood pressure. Clinically, visceral pain is extremely prevalent in the general population, yet compared with somatic pain its mechanisms are poorly understood.

One of the reasons that visceral pain research trails behind somatic pain research is the fact that for many years it was thought that the viscera were not capable of encoding pain because clinical observations showed that cutting or burning visceral tissue often did not induce a painful response. Subsequently, it was discovered that mechanical, electrical, chemical, and ischemic stimuli could all induce visceral pain both in humans and animals, and this has led to extensive research that is aimed at understanding the mechanisms of visceral pain.

In this review, we provide an overview of the advances in human visceral pain research over the last decade, reviewing data from studies of the gastrointestinal (GI) tract. We aim to provide a brief summary of the major clinical problem faced by GI healthcare professionals and scientists when dealing with painful functional GI disorders (FGID), outline the proposed mechanisms of aberrant visceral pain processing, and highlight recent studies of the GI tract that have utilized commonly used electrophysiological techniques in tandem with state of the art functional brain imaging to study brain-gut interactions.

Scale of the clinical problem

FGID are a group of symptom-based GI conditions that are characterized by a variety of abdominal symptoms, including changes in bowel habit, indigestion, nausea, early satiety, and, most commonly, pain. FGID account for 40% of all new referrals to GI clinics, and, despite extensive clinical investigation and expanding research in this area, their pathophysiology remains uncertain. The lack of a firm diagnosis in FGID leads to increased patient morbidity, which in turn results in frequent attendance to hospital clinics. This combination of extensive investigation and frequent hospital attendance exerts a considerable financial strain on healthcare resources and the economy. A recent socioeconomic study has estimated that the combined cost of healthcare utilization and job absenteeism related to FGID is $41 billion per annum in the eight leading Western economies (6).

An example of the type and severity of visceral pain endured by some patients with FGID is angina pectoris, which...
is a symptom usually associated with myocardial ischemia and is characterized by severe central chest pain, which radiates to the neck and upper limbs and can be associated with anterior chest wall tenderness. Up to a third of patients presenting with angina-like symptoms have no evidence of cardiac disease, and these patients are given the label of noncardiac chest pain (NCCP). NCCP is just one subset of FGID; however, in 1987, the annual medical expense for patients with angina-like pain and normal coronary arteries in the US was over $700 million, and this figure is likely to have grown substantially in subsequent years.

**Proposed pathophysiological mechanisms of FGID**

The predominant reason why FGID patients seek medical attention is chronic, episodic pain. Pain comprises two distinct dimensions: sensation and affect. Pain sensation comprises the sensory discriminatory components of pain processing, whereas pain affect consists of a combination of emotional and cognitive appraisals related to the pain experience (15). It has long been the goal of clinicians to understand the role of these dimensions in the pathophysiology of FGID. To achieve this, research has focused on three main aspects of the visceral pain matrix thought to be important in the generation and perception of pain.

**Peripheral sensitization.** The first and most obvious area to investigate has been within the gut itself. Unlike most internal organs, the gut is constantly exposed to a combination of potentially pathogenic organisms and a cocktail of digestive chemicals. It is therefore not surprising that damage commonly occurs in the form of infection (acute gastroenteritis) or inflammation (esophagitis, inflammatory bowel disease). However, although treatment of these conditions can appear to be successful, many patients develop prolonged symptoms after the original insult has passed.

Recent research suggests that this persistence of pain may be due to sensitization of gut primary afferents (peripheral sensitization) by inflammatory mediators such as K⁺, H⁺, ATP, bradykinin, and prostaglandins, which activate and sensitize nociceptive afferent nerves. New techniques are available to study these processes in biopsies taken from patients with chronic visceral hypersensitivity states without evidence of overt inflammation and have shown demonstrable changes indicative of peripheral sensitization. (10) Therefore, peripheral sensitization may also contribute to visceral hypersensitivity in FGID.

**Central sensitization.** A secondary consequence of peripheral sensitization is the development of an area of hypersensitivity in the surrounding uninjured tissue. This phenomenon is due to changes in the activity of spinal afferents and is called central sensitization. Central sensitization is sustained by phosphorylation of N-methyl-D-aspartate receptors expressed in dorsal horn neurons, which induces changes in the receptor kinetic properties and increases its sensitivity to synaptically released glutamate. This leads to an increase in the excitability and the receptive fields of the spinal neurons and results in recruitment and amplification of both nonnociceptive and nociceptive inputs from the adjacent healthy tissue (for reviews, see Refs. 19 and 20).

Evidence that central sensitization is a component of somatic hypersensitivity has been provided by well-established models of human somatic pain. Cutaneous nociceptive activation with capsaicin or mustard oil induces allodynia/hyperalgesia with demonstrable increases in afferent pathway sensitivity. Animal studies involving direct electrophysiological recordings from spinal neurons suggest that central sensitization may also be an important mechanism in generating visceral hypersensitivity and pain. Until recently, similar human studies have not been possible due to a lack of available experimental models and noninvasive neurophysiological techniques to assess visceral afferent pathways.

**Psychological and psychiatric factors.** The affective dimension of pain combines the degree of unpleasantness perceived with the emotions and cognitive appraisals associated with its present and future implications. It has long been recognized that cognitive modulation of pain can have dramatic effects on its perception. In FGID, a high incidence (50–80%) of psychological disorders such as heightened anxiety, depression, somatization, dysthymia, and panic disorders have been reported (5).

The role that attentional state plays in modifying pain is a psychological variable that has been most commonly studied. Experiments have shown that pain is perceived as less intense when we are distracted from it and, in most cases, more intense when we focus our attention on it. In FGID it has been shown that patients often selectively attend to sensations that arise from the gut, and it has been shown that this is an important factor in sustaining symptoms.

Reasons why these patients selectively attend to gut sensations include factors such as exposure to family illness. For instance, if a close relative has previously suffered a myocardial infarction, then symptoms of chest pain or even sensations arising from the chest that would normally be innocuous are associated with serious disease. The anxiety associated with this disease attribution will in turn increase levels of arousal and attention, and this has been shown to result in greater awareness and poorer tolerance of both experimental and endogenous gut sensations (18).

**Investigating extrinsic GI afferent pathways**

Despite the high incidence of GI symptoms in neurological conditions and the complex intrinsic and extrinsic innervation of the GI tract, there is a dearth of available information related to the neurophysiological basis of visceral sensation and pain. However, novel adaptations of commonly used neurophysiological techniques have allowed us to begin to noninvasively investigate the integrity and characteristics of GI afferent pathways, and slowly our knowledge in this area is expanding. For about 50 years, neurophysiologists have used evoked
potentials (EP) to study somatosensory, visual, auditory, and pain pathways. This technique involves the brief presentation of a sensory stimulus that is time and phase locked to the recording of the electroencephalogram (EEG) via surface electrodes placed on the scalp. The event-related signal is small in amplitude but occurs at the same moment in time following each stimulus, whereas the large-amplitude background EEG is randomly occurring. To extract the desired signal, repeated stimuli are given and the subsequent brain activity is averaged. This reduces the unwanted EEG while enhancing the event-related EP (11).

The first EP responses to stimulation of the GI tract were recorded in 1989, and an example of how signal averaging is used to improve the signal-to-noise ratio of esophageal EPs (EEPs) can be seen in Fig. 1A. Once the feasibility and reproducibility of visceral EP recording had been established, subsequent studies revealed that they could be recorded throughout the GI tract, and this technique has developed as a powerful tool in the GI researchers’ armory.

Recent studies have shown that not only can EP be successfully recorded from many GI regions (Fig. 1B), but the characteristics of the response correspond to known physiological differences in their innervation and function. For instance, despite the rectum lying distal to the esophagus, the latency of the rectal EP components are shorter and the response is elicited at significantly lower stimulation intensities. This is entirely in keeping with the role of the rectum as a sensory organ with rich afferent innervation essential for maintaining continence, whereas conscious sensations rarely arise from the esophagus (8).

Previous studies of visceral hypersensitivity relied on descriptive methods of reporting visceral sensation, and although great care was taken to eliminate subjective factors from introducing response bias, no truly objective measures of sensation have been designed. An obvious question therefore was whether visceral EP could be used as an objective measure of visceral pain. To address this question, several groups examined the effects of increasing the stimulation intensity on the amplitude and latency of the EEP components.

These studies showed that as stimulation intensity and sensory perception increased there was an associated reduction in the latency and increase in amplitude of the EEP components (Fig. 1C). This phenomenon is common across all EP modalities and reflects the recruitment of an increasing number of afferents (9). It therefore allowed a correlation of an increase in the reported sensation with an objective, neurophysiological measure, thus reducing the inherent response bias commonly encountered in clinical evaluation of visceral pain.

A comparison of EEP elicited by electrical and mechanical stimulation showed that both responses were mediated by thinly myelinated Aδ-fibers, that both produced responses of identical morphology, and that the latency difference between the first mechanical and electrical EEP component of ~50 ms was due to the physical delay encountered during balloon inflation, not activation of different fiber types. This is not to say that unmyelinated C-fibers are not activated by esophageal stimulation, just that they do not contribute to the early response complex recorded with EEP (9).

**FIGURE 1.** A: effect of signal averaging on the esophageal evoked potential (EEP). It can be seen that following 1 stimulus the EEP is hidden in the large-amplitude background electroencephalogram (EEG). However, as subsequent epochs are averaged, the commonly occurring event-related signal increases while background EEG diminishes. We have found that recording the average of 200 stimuli acquired in 4 runs of 50 stimuli gives us our optimal signal-to-noise for EEP. B: visceral evoked potential (EP) recorded from different regions of the gastrointestinal (GI) tract. There is a common morphology for each GI region; however, differences in stimulation intensity needed to evoke response and resultant conduction velocity correspond to known differences in their function and physiology. C: effect of increasing stimulation intensity and amplitude and latency of EEP. As stimulation intensity increases, there is a corresponding decrease in latency and increase in amplitude of the EEP components.
Importantly, the amplitude of mechanically evoked EEP was smaller than that seen in response to electrical stimulation. It is known that the amplitude of the EEP increases with increased afferent recruitment. These amplitude differences could therefore be explained by the fact that mechanical stimulation is specific to mechanosensitive afferent receptors, whereas electrical stimulation activated all afferents regardless of modality, hence leading to greater afferent recruitment.

Interestingly, visceral EP are similar in nature to somatic pain EP responses elicited by thermal cutaneous laser stimulation. Like esophageal stimulation, laser stimulation selectively activates nociceptive afferents, namely thinly myelinated Aδ- and unmyelinated C-fibers. The resultant laser EP response shares several other characteristics with EEP: it habituates over time, it is maximally recorded at the vertex, and changes in the latency of components can occur with alteration of the level of vigilance/attention afforded to the stimulus (1).

Therefore, in summary, over the last ten years the feasibility, reproducibility, and physiological relevance of visceral EP has been established. For the first time GI scientists have at their disposal a clinical research tool that allows them to objectively and directly assess the neurophysiology of the central nervous system control of the GI tract in humans.

The visceral-cortical pain matrix

Each component of the visceral EP represents a summation of cortical activity related to specific steps in the cortical processing of visceral sensation and pain. Because pain involves so many integrated aspects, it is clear that it is a result of a complex interaction of many brain regions. This has been demonstrated for somatic pain by using PET and fMRI, which have revealed activation of a network of cortical and subcortical structures, and this has been named the pain matrix (17).

Therefore, during the next stage in the evolution of clinical GI neuroscience, attempts were made to identify the neuroanatomic representation of the visceral pain matrix. The use of complementary techniques such as fMRI and PET has led to the identification of a network of brain areas that process visceral sensation. These studies suggest that, unlike somatic sensation and pain, which has a strong homuncular representation in the primary somatosensory cortex, visceral sensation is primarily represented in the secondary somatosensory cortex whereas its representation in primary somatosensory cortex is vague. This difference could account for the poor localization of visceral sensation compared with somatic sensation.

However, in a manner similar to that of somatic sensation, visceral sensation is represented in the paralimbic and limbic structures such as the insular, anterior cingulate, and prefrontal cortices (2). These areas are likely to mediate the affective and cognitive components of visceral sensation. Figure 2 shows a series of surface-rendered images that depict the cortical representation of esophageal sensation in response to mechanical stimulation.

fMRI has also been used to study the cortical representation of anorectal stimulation. In this study, rectal (visceral) stimulation resulted in bilateral activation of the inferior primary somatosensory, secondary somatosensory, sensory association, insular, periorbital, anterior cingulate, and prefrontal cortices. Anal (somatic) canal stimulation resulted in activation of areas similar to rectal stimulation, but the primary somatosensory cortex was activated at a more superior level, and there was no anterior cingulate activation.

This study concluded that anal and rectal sensation resulted in a similar pattern of cortical activation, including areas involved with spatial discrimination, attention, and affect. The differences in sensory perception from these two regions.

FIGURE 2. Group functional magnetic resonance imaging (fMRI) image showing bilateral activation of the sensorimotor cortex following painful mechanical stimulation of the esophagus.
could be explained by their different representation in the primary somatosensory cortex. The fact that the anterior cingulate cortex was only activated by rectal stimulation suggests that the viscera have a greater representation on the limbic cortex than somatic structures, and this may help to explain the greater autonomic responses evoked by visceral sensation compared with somatic sensation (7). Despite the obvious similarities between the cortical representation of somatic and visceral sensation/pain, subtle differences remain, and further studies are needed to discern these in more detail.

Although these studies represent a major advance in our understanding of visceral sensory and pain processing, it is unlikely that functional brain imaging techniques will be used routinely as a standard clinical investigation for FGID. However, if the functional and neuroanatomic significance of the visceral EP components could be delineated, then this technique could be used for routine bedside assessment in patients with FGID.

Magnetoencephalography (MEG) is a technique that allows us to detect the minute magnetic fields generated by active groups of cortical neurons. MEG has comparable spatial resolution with PET and fMRI but directly reflects changes in neuronal activity on a millisecond-by-millisecond basis. Recent advances in MEG analysis have made it feasible to study the visceral-cortical pain matrix in real time, which may allow us to identify the sequence of activation of individual cortical regions. This temporal information can be related to the scalp-recorded EP response, and the cortical sources involved in the generation of the separate visceral EP components can be identified. Thus we would be able to see which components relate to sensory discriminatory aspects of pain against those involved in pain affect. This would give us the opportunity to identify specific neurophysiological abnormalities in individual FGID patients without the need for expensive neuroimaging techniques.

Central nervous system modulation of visceral sensation and pain

As the robustness of these new functional brain imaging and neurophysiological techniques has been proven, so interest has turned to developing experimental models that allow us to modulate this system and give us further insight into the mechanisms of visceral hypersensitivity. The following section describes two of these models.

**Does peripheral and central sensitization contribute to visceral hypersensitivity?** As described earlier, one of the proposed mechanisms of visceral hypersensitivity is peripheral and central sensitization of visceral afferents. This phenomenon has been well studied in somatic pain; however, we have recently developed a similar model in the esophagus that allows us to examine these processes in both healthy subjects and patients with NCCP.

We infused 0.15 M HCl into the distal esophagus for 30 min. We then measured pain thresholds at the site of infusion as well as in the proximal esophagus, which had not been exposed to acid. The hypothesis was that peripheral sensitization will be induced at the site of infusion, which will in turn reduce pain thresholds in the non-acid-exposed proximal esophagus due to central sensitization of spinal afferents.

These studies revealed that both peripheral and central sensitization could be induced following acid but not saline infusion and that these changes were exaggerated in patients with NCCP (Fig. 3) (16). Additionally, we provided objective evidence for changes in the central visceral afferent pathway by recording EEP before and after acid infusion from the proximal esophagus. These studies revealed that, despite using the same stimulation throughout, the latency of the EEP component...
reduced following acid, indicating a potentiation of the response (Fig. 4). We therefore concluded that peripheral and central sensitization contribute to the development of visceral hypersensitivity and may be important mechanisms in FGID.

Do emotions influence our perception of visceral stimuli? Negative mood states, such as fear or sadness, are often associated with abnormal sensory perception, such as abdominal pain (4). In this study, we examined the effects of negative emotional context on the perception of visceral sensations. It has been demonstrated that human facial expressions (considered to be the primary source for conveying the emotional valence regarding a particular situation) depicting different emotions activate different brain neuronal networks. We therefore employed fearful and neutral facial expressions from a standardized series to provide negative and neutral emotional contexts respectively while healthy subjects experienced phasic, nonpainful esophageal stimulation. We then compared the brain activation patterns by using fMRI.

These studies revealed that activation within the right insular and bilateral dorsal anterior cingulate cortex was significantly greater during esophageal stimulation with fearful rather than neutral facial expressions (Fig. 5). These changes also correlated with behavioral ratings for increases in anxiety and discomfort, providing evidence for a modulation of neural responses and perceived discomfort during nonpainful visceral stimulation by negative emotional context. These findings support the role of negative emotions as a mechanism of altered pain perception in FGID. (14)

Functional brain imaging in FGID

There have been a handful of studies so far that have compared cortical activation patterns in healthy subjects and patients with irritable bowel syndrome (3, 12). Unfortunately, because current diagnosis of FGID relies on symptoms rather than specific pathophysiological abnormalities, the group was heterogeneous, and this was reflected by the variability of the reported data, which ranged from increased cortical activation at one end of the spectrum to no activation at all! It is clear from these studies that FGID patients need to be subdivided into homogenous groups based on common neurophysiological profiles. Only when we achieve this can specific hypothesis-testing experiments be designed and the true value of functional brain imaging in FGID be realized.

Concluding remarks

It is clear that the pathophysiology of unexplained pain in FGID is complex and multidimensional, incorporating biological, physiological, and psychological/psychiatric components. Advances in GI neuroscience over the last decade have finally provided us with an opportunity to bring together basic scientists, neuroscientists, clinicians, and healthcare providers to take research from bench to bedside. It is now imperative that we take an interdisciplinary approach to investigating the mechanisms of GI dysfunction in FGID and develop pathophysiological models that allow us to identify the specific etiology of symptoms in individual patients. Specifically targeting the management and treatment of FGID patients will not only allow us to alleviate symptoms more effectively but also to utilize healthcare resources more efficiently.

A. R. Hobson is funded by the Lord Dowding Fund for Humane Research

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