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Topical review

Mechanisms of visceral pain in health and functional gastrointestinal disorders

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HIGHLIGHTS

- Functional gastrointestinal disorders (FGIDs) are a heterogeneous group of disorders.
- Aetiology remains an enigma but visceral hypersensitivity causes pain in FGIDs.
- Peripheral and central mechanisms cause visceral hypersensitivity and pain.
- Inflammatory mediators activate and sensitize normal and silent nociceptors peripherally.
- Changes in CNS pain modulating mechanisms cause central hyperalgesia.
- Gastrointestinal microbiota is an ecosystem modulating motility and visceral perception.
- Connective tissue abnormalities affect gut mobility and sensations.
- Gastrointestinal neuromuscular disorders disturb gut motility and cause transient dilatations.

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ABSTRACT

Background and aims: Chronic visceral pain is common both in patients with identifiable organic disease and also in those without any structural, biochemical or immunological abnormality such as in the functional gastrointestinal disorders (FGIDs). We aim to provide a contemporaneous summary of pathways involved in visceral nociception and how a variety of mechanisms may influence an individual's experience of visceral pain.

Methods: In this narrative review, we have brought together evidence through a detailed search of Medline in addition to using our experience and exposure to recent research developments from ourselves and other research groups.

Results: FGIDs are a heterogeneous group of disorders whose aetiology largely remains an enigma. The germane hypothesis for the genesis and maintenance of chronic visceral pain in FGIDs is the concept of visceral hypersensitivity. A number of peripheral and central mechanisms have been proposed to account for this epiphenomenon. In the periphery, inflammatory mediators activate and sensitize nociceptive afferent nerves by reducing their transduction thresholds and by inducing the expression and recruitment of hitherto silent nociceptors culminating in an increase in pain sensitivity at the site of injury known as primary hyperalgesia. Centrally, secondary hyperalgesia, defined as an increase in pain sensitivity in anatomically distinct sites, occurs at the level of the spinal dorsal horn. Moreover, the stress responsive physiological systems, genetic and psychological factors may modulate the experience of visceral pain. We also address some novel aetiological concepts in FGIDs, namely the gastrointestinal microbiota, connective tissue abnormalities and the gastrointestinal neuromuscular disorders. Firstly, the gastrointestinal microbiota is a diverse and dynamic ecosystem, that safeguards the host from external pathogens, aids in the metabolism of polysaccharides and lipids, modulates intestinal motility, in addition to modulating visceral perception. Secondly, connective tissue disorders, which traditionally have been considered to be confined largely to the musculoskeletal system, have an increasing evidence base demonstrating the presence of visceral manifestations. Since the sensorimotor apparatus of the GI tract is embedded within connective tissue it should not be surprising that such disorder may result in visceral pain and abnormal gut motility. Thirdly, gastrointestinal neuromuscular diseases refer to a

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heterogeneous group of disorders in which symptoms arise from impaired GI motor activity often manifesting as abnormal transit with or without radiological evidence of transient or persistent dilation of the viscera. Although a number of these are readily recognizable, such as achalasia or Hirschsprung's disease, the cause in a number of patients is not. An international working group has recently addressed this "gap", providing a comprehensive morphologically based diagnostic criteria.

Conclusions/implications: Although marked advances have been made in understanding the mechanisms that contribute to the development and maintenance of visceral pain, many interventions have failed to produce tangible improvement in patient outcomes. In the last part of this review we highlight an emerging approach that has allowed the definition and delineation of temporally stable visceral pain clusters, which may improve participant homogeneity in future studies, potentially facilitate stratification of treatment in FGID and lead to improvements in diagnostic criteria and outcomes.

Contents

1. Background

Visceral pain is a highly variable experience in both health and disease. Chronic visceral pain is common, occurring in patients with organic disease and also in those without any identifiable structural, biochemical or immunological abnormality such as in the functional gastrointestinal disorders (FGIDs). FGIDs are a heterogeneous group of disorders in which a complete understanding of the pathophysiology remains elusive. A central defining feature of the FGID is chronic visceral pain, which is a major factor in motivating patients to seek healthcare and causes a significant reduction in quality of life [1]. Within the European Union, approximately 100 million people are affected by chronic somatic and visceral pain, with 28 million suffering from regular severe pain [2]. This prevalence is associated with a marked societal burden, with 60% sufferers having consulted their doctors between two and nine times in the preceding six months, and approximately 1/5th of patients unable to work [3]. The effective management of visceral pain in FGID is problematic despite substantial progress in basic gastrointestinal (GI) research aimed at identifying the responsible mechanisms [4]. However, the successful translation of this research into improvements in patient outcomes has been limited arguably because a significant proportion of our understanding of visceral nociception has been extrapolated from somatic pain studies [5].

2. Aims

For the purposes of this review we aim to provide the reader with a state of the art update of mechanisms of visceral pain in health but also to provide clinical context through special reference to FGID.

3. Methods

In this narrative review, we have brought together many diverse strands of research through searching the PubMed interface of Medline in addition to using our experience and exposure to recent research developments from colleagues and collaborators across the world. In order to contextualize visceral pain we commence this review with a summary of the sensory pathways from the GI tract to the brain via the spinal dorsal horn that facilitate visceral nociception. In addition, we examine the burden of chronic unexplained visceral pain, and explain how such pain may develop through either peripheral or central sensitization. We also discuss how an individual's experience of visceral pain may be modulated by psychology, genetic factors and the physiological stress responsive systems as well as describing some novel aetiological concepts. Finally we shall introduce, what we believe to be, an exciting and emerging theory in visceral nociceptive research – the definition and delineation of human pain clusters.

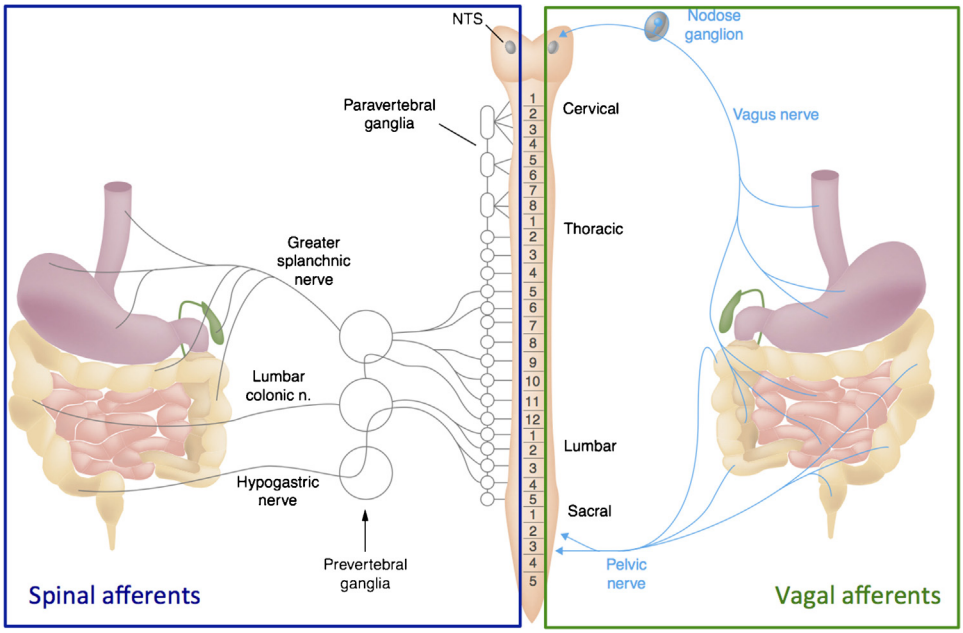

Fig. 1. Schematic representation of the sensory innervation of the GI tract. Left: (blue box) – spinal afferent pathways to the spinal cord are via prevertebral and paravertebral ganglia. Right: (green box) vagal afferents supply the entirety of the GI tract except the distal 2/3rd of the colon, which is innervated by pelvic nerve afferents. The input of these pathways to the spinal cord is via the nodose and dorsal root ganglia respectively, onto the nucleus tractus solitarius (NTS).
From Blackshaw and Gebhart with permission [6].

4. Results

4.1. Sensory pathways from the gastrointestinal tract to the spinal dorsal horn

The GI tract receives a dual innervation from two extrinsic pathways known as vagal and spinal afferent pathways (see Fig. 1). These pathways are complemented by an intrinsic nervous system located within the GI tract known as the enteric nervous system. Vagal afferent endings are more numerous in the proximal GI tract and their axons project directly to the brainstem with their cell bodies located in the nodose or jugular ganglia. In contrast, spinal afferent endings are distributed throughout the GI tract, and course in the splanchnic nerves to the thoracolumbar spinal cord and in the pelvic nerves to the sacral portion of the spinal cord. Spinal afferent axons synapse with the spinal dorsal horn and their cell bodies are located in the dorsal root ganglia [6]. The GI tract has several types of afferent fibres that can be usefully classified according to their response to either innocuous/physiological or noxious stimuli, or both. For instance, there are fibres that respond to tactile, chemical, distensile or contractile stimuli at physiological or noxious levels. In addition to these specific nociceptors, it has been proposed that muscular-mucosal afferents may also function as nociceptors and are referred to as wide dynamic range afferents as they initially respond to low threshold stimuli but heighten their response to increasing distension into the noxious range. It is presumed that these provide the ability to "grade" the spectrum of visceral sensation from gas to urge to mild discomfort to frank pain [7].

4.2. Central pathways from dorsal horn to higher centres

The spinal dorsal horn is a central and critical junction within visceral nociceptive pathways as the afferent ascending signals from the periphery are constantly modulated by local and descending interneurons [8]. The spinal dorsal horn may thus accentuate, or indeed attenuate, this ascending volley of information through a number of localized viscera-visceral and viscera-somatic reflexes [9]. The advent of functional neuroimaging has allowed the central aspects of visceral nociception to be studied in an objective manner. This body of work has led to significant advances in our understanding of the central circuitry involved in mediating and maintaining visceral pain. Spinal afferents, synapsing on the spinal dorsal horn, project second order neurons to higher centres through three distinct long tract pathways: the dorsal column pathway, parabrachial pathway and spinothalamic tract. In combination with projections from the nucleus of the solitary tract which receives input from vagal afferents via the nodose ganglia, spinoparabrachial projections are transmitted to limbic and cognitive higher brain centres including the amygdala, hypothalamus and periaqueductal grey [10]. These centres largely facilitate the cognitive evaluative aspects of visceral pain sensation. Conversely, the sensory discriminatory aspects of visceral pain are derived from thalamic projections to the insula and somatosensory cortices whilst the medial thalamic nuclei are posited to have a greater role in affective and motivational aspects, prior to projecting onwards to the prefrontal and anterior cingulate cortex [11]. Interestingly, an important quantitative meta-analysis of functional neuroimaging studies examining brain activation by rectal distension reported that patients with irritable bowel syndrome (IBS), itself characterized by chronic visceral pain associated with alterations in bowel habit, have greater activation of regions associated with emotional arousal and endogenous pain modulation whereas healthy controls have greater activation in cognitive modulatory regions [12].

4.3. The functional gastrointestinal disorders as examples of chronic visceral pain syndromes

Arguably, the FGIDs are the most prevalent examples of chronic visceral pain syndromes. FGIDs represent a considerable burden to healthcare economies in both primary and secondary care [13,14]. The Rome multi-national consensus defines FGID as "*variable combinations of chronic or recurrent gastrointestinal symptoms which are not explained by structural or biochemical abnormalities* [1]." The understanding of the processes that underpin the genesis of

symptoms in FGIDs remains incomplete. The most prevalent example of a FGID is IBS, with a global prevalence of 5–20% [15]. On account of the current paucity of effective treatments for managing chronic visceral pain in FGIDs the inevitable result is often symptom chronicity, patient dissatisfaction, disenfranchisement, and significant morbidity. Moreover, the direct and indirect healthcare costs associated with FGIDs have been estimated to be in the order of $34 billion in the 7 largest western healthcare economies [1,16]. In the following section we shall highlight the putative mechanistic basis of chronic visceral pain, namely peripheral sensitization, central sensitization and their modulating factors relating these to frequently encountered examples of FGIDs in clinical practice.

4.4. Peripheral sensitization as a mechanism of visceral pain

Noxious stimuli may cause the peripheral release of several inflammatory mediators such as K^+, H^+, adenosine triphosphate, 5-hydroxytryptamine, bradykinins and prostaglandins [17,18]. These mediators may elicit a number of effects, including the activation and peripheral sensitization of nociceptive afferent nerves by reducing their transduction thresholds and by inducing the expression and recruitment of hitherto silent nociceptors. The main consequence of these inflammatory mediators is an increase in pain sensitivity at the site of injury known as primary hyperalgesia [19]. A number of ion channels, neurotransmitter receptors and trophic factors have been implicated in the development of peripheral sensitization. Whilst it is beyond the scope of this review to examine all of the mechanisms studied in the literature to date, we will highlight, in our opinion, some of the more important recent advances in our understanding of the underlying molecular features of peripheral sensitization: the transient receptor potential vallinoid receptors (TRPV), and the protease activated receptors (PAR).

4.4.1. Transient receptor potential vallinoid receptors

TRPV1 is an ion channel that serves a diverse range of sensory functions such as temperature sensing and hearing [20,21]. The TRPV1 receptor was first identified and subsequently cloned in the late 1990s and is ubiquitously expressed on small to medium sized neurones [22]. The TRPV1 receptor may be activated by capsaicin and heat and is postulated to play an important role in mechano-transduction within the GI tract [20,23]. Upon activation, the TRPV1 receptor evokes a sensation of burning and pain and when associated with concomitant release of substance P, neurogenic inflammation. As hydrogen ions strongly potentiate this activation it is not surprising that this ion channel has been widely studied in gastro-oesophageal reflux disease, a disorder where excess acid exposure in the distal oesophagus is central to the pathogenesis [24,25]. There is accumulating evidence in humans linking increased TRPV1 expression with visceral hypersensitivity [26]. Interestingly, TRPV1 receptor antagonists have been found to ameliorate visceral hypersensitivity in a rat model [27]. These observations have led to considerable interest in the development of TRPV1 antagonists [28]. For instance, Krarup et al. reported a randomized, placebo-controlled, double-blinded, crossover study investigating the effect of a TRPV1 antagonist (AZD1386) on experimentally induced oesophageal pain. Whilst pain thresholds to modalities such as mechanical and chemical stimulation were unaffected, AZD1386 did increase pain thresholds to heat stimuli within the oesophagus [29]. In a recent study, the effects AZD1386 were investigated in patients with acute pain following a dental extraction [30]. Compared to placebo, perceptible pain relief was significantly faster following AZD1386 although these differences were not appreciable when compared to naproxen.

4.4.2. Protease activated receptors

Four types of PAR have been described in the literature. Of note, PAR-1 and PAR-2 are expressed on spinal afferents and contain calcitonin gene related peptide [31]. PAR-2 receptors are activated by mast cell tryptase and are G-protein coupled receptors [32]. PAR-1 is activated by a number of mediators including thrombin and trypsin and are expressed throughout the GI tract [33]. Interestingly, increased expression of PAR-1 has been demonstrated in patients with inflammatory bowel disease thereby providing an interesting mechanistic insight into inflammation induced sensitization [34]. PAR-4 is activated by thrombin, trypsin and the enzymatic protein cathepsin G, but can also be selectively activated by a number of small synthetic peptides. Recent evidence suggests that PAR-4 is an endogenous analgesic, which can modulate nociceptive responses in normal and inflammatory disorders [35].

4.5. Central sensitization as a mechanism of visceral pain

Sarkar et al. demonstrated the concept of central sensitization in a reproducible human oesophageal model in which hydrochloric acid is infused into the distal oesophagus [36]. Pain thresholds, to electrical stimulation, were not only reduced in the acid exposed distal region but also in the adjacent unexposed proximal region thereby suggesting the development of secondary hyperalgesia and central sensitization (see Fig. 2).

Using pharmacological interventions with this model has provided some important insights into the molecular mechanism involved. For instance, it has been demonstrated that administration of a prostaglandin receptor antagonist prior to acid infusion blocks the subsequent development of oesophageal hypersensitivity suggesting that prostaglandins play an important role in mediating peripheral and central sensitization [37]. The n-methyl D-aspartate receptor has been proposed as a critical molecular factor in the development and maintenance of central sensitization, through interactions occurring at the spinal dorsal horn [38]. Interestingly, antagonism of n-methyl D-aspartate receptors can prevent the development of acid induced central sensitization within the oesophagus [39].

4.6. Evidence linking peripheral and central sensitization in functional gastrointestinal disorders

Chronic episodic abdominal pain and discomfort cause appreciable morbidity in FGIDs and are integral components of the diagnostic criteria in these disorders. It has been 35 years since it was first reported that a proportion of patients with FGIDs may display elevated pain sensitivity to experimental gut distension – visceral pain hypersensitivity (see Fig. 3) [40–43]. Whether these observed alterations in visceral sensitivity are part of a global phenomenon of generalized sensory dysfunction is controversial [36,44–46]. Visceral pain hypersensitivity has become the germane hypothesis to account for chronic pain in FGIDs. The putative pathophysiology of visceral pain hypersensitivity may be conceptualized as being due to aberrant processes that may arise at any level of the visceral nociceptive pathway (neuraxis) encompassing both peripheral and central sensitization.

Arguably, the prototypical example of FGIDs in which the aforementioned mechanisms predominant in the development of chronic visceral pain is post-infectious IBS (PI-IBS) [49]. Whilst the overwhelming majority of individuals who develop bacterial gastroenteritis have acute self-limiting symptoms, between 4 and 32% of patients develop symptoms consistent with IBS that outlast the initial infectious insult [50]. Chronic symptoms, such as abdominal pain, bloating, and diarrhoea, have been documented after a variety

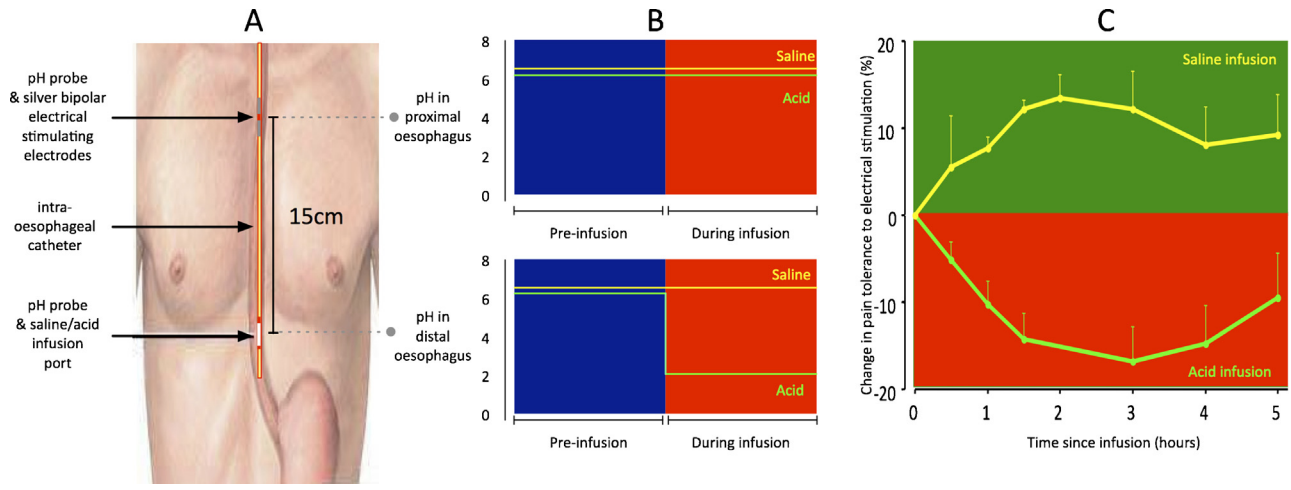

Fig. 2. A schematic representation of the oesophageal pain hypersensitivity model. From left to right: Panel A – a catheter is placed in the oesophagus which has a proximal pH probe and silver bipolar electrical stimulation electrodes to measure oesophageal pain sensitivity and a distal pH probe and infusion port. Panel B – subjects are randomized to received either a saline or acid infusion. As expected when saline is infused there is no change in pH in either the proximal or distal oesophagus, whereas there is a demonstrable drop in pH in the distal, but not in the proximal, oesophagus during acid infusion. Panel C – pain thresholds in the proximal oesophagus, which has not been exposed to acid, show decreased pain sensitivity (shaded green area) due to habituation following saline infusion but following acid infusion there is increased pain sensitivity (shaded red area) due to central sensitization.
Adapted from [36].

of enteric pathogens including *Campylobacter*, *Salmonella*, *Shigella* strains and *Escherichia coli*. Indeed, public health calamities such as the *E. coli* outbreak in Walkerton, Ontario have afforded researchers the opportunity to prospectively study the natural history, pathophysiology and genetic susceptibility of PI-IBS at the population level [51]. Although there is an absence of universally applicable pathophysiological features, intestinal inflammation, alterations in GI motility and permeability have all been implicated. Furthermore, hyperplasia of serotonin-containing enterochromaffin cells, intestinal T lymphocytes, mast cells, and pro-inflammatory cytokines within the mucosa have been demonstrated [52]. Given the emerging evidence that PAR mediate peripheral sensitization, it is not surprising that their function as possible mediators of PI-IBS has been examined. Han et al. investigated the expression of PAR(2) and PAR(4) in the colonic mucosa of patients with PI-IBS, focusing on correlation with mast cell activation status [53]. It was shown that the immune-reactivity of PAR(4) decreases, while the activity of mast cells increases in post-infectious irritable bowel syndrome patients in comparison to healthy controls offering a potential target for therapy.

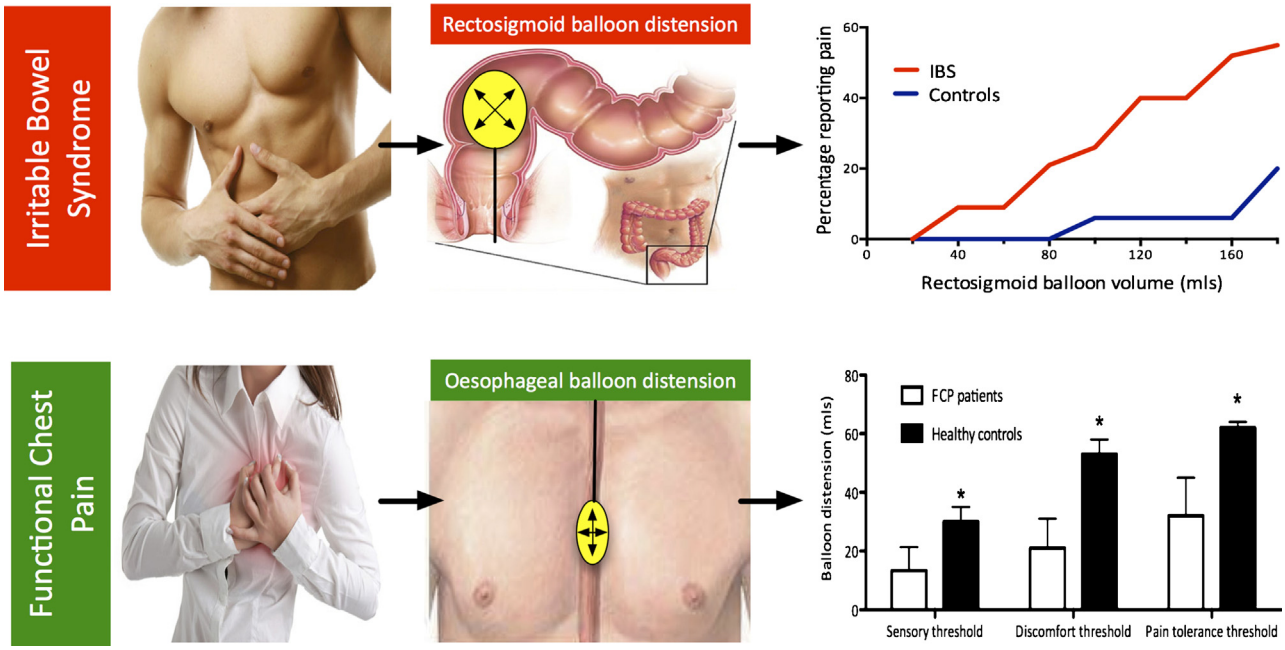

Fig. 3. Evidence for the concept of visceral pain hypersensitivity in functional gastrointestinal disorders. Top – IBS patients and healthy controls were evaluated for their pain thresholds in response to progressive stepwise (ramp) distension of a 5 cm balloon placed in the recto-sigmoid junction. A greater proportion of IBS patients reported pain than the healthy subjects [47]. Bottom – in functional chest pain (FCP) patients and healthy controls sensory, discomfort and pain tolerance thresholds were measured in response to oesophageal distension. Patients had lower thresholds across all three parameters [48].

Although elevated expression of TRPV1 in rectal biopsies has been demonstrated, a recent study by van Wanrooij et al. addressed the important question of its role in mediating visceral hypersensitivity [54]. In this study, IBS patients and healthy controls underwent assessment of sensitivity to rectal distension before and after the intra-rectal application of capsaicin (to sensitize the TRPV1 receptor). In addition, rectal biopsies were examined for TRPV1 expression. Whilst approximately half of the IBS patients demonstrated visceral hypersensitivity to rectal distension, the investigators did not demonstrate any evidence for up-regulation of TRPV1 expression. Despite these results, it remains a speculative possibility that there is an increase in the receptor sensitivity rather than up-regulation per se.

4.7. Modulation of visceral pain

There is dynamic bidirectional communication from the GI tract to the brain and back again, often referred to in the literature as the brain–gut axis. There are a number of "top-down" interactions and influences on the brain–gut axis [55] that modulate visceral pain perception and experience such as psychological traits, genetic factors and the stress responsive physiological systems. In combination with peripheral and central sensitization these modulating factors can lead to a heighten perception, and a perpetuation of, visceral pain.

4.7.1. Psychological and genetic influences

Psychological comorbidity such as depression, anxiety, somatization and hypochondriasis are common extra-GI features of FGIDs [56,57]. In animal models, studies have shown that adverse early life events are risk factors for the development of chronic visceral pain in adulthood [58]. In patients with IBS, pain amplification and hypervigilance might result from altered affective-motivational modulation of the pain response. Elsenbruch et al. investigated the effects of emotional context on the behavioural and neural response to visceral stimuli in IBS patients using functional magnetic resonance imaging to assess neural responses to non-painful and painful rectal distension in IBS patients against healthy controls [59]. IBS patients had disrupted of emotional modulation of neural responses to visceral stimuli, possibly reflecting the neural basis for altered visceral interoception by stress and negative emotions. Therefore, it maybe reasonably surmised that anxiety and negative emotional context may influence the perception of visceral pain. Furthermore, adverse life events, such as a history of sexual abuse, can modulate visceral pain sensitivity [60–62]. The increased recognition and appreciation of PI-IBS as a clinical entity has facilitated the prospective examination of role of psychological factors in FGIDs. Early data from the Sheffield group, subsequently confirmed by others, has shown that at the time of the initial infectious illness those who had higher scores for anxiety, depression, somatization, and neuroticism were more likely to develop symptom chronicity [63].

FGIDs display a certain degree of heritability with twin cohort studies suggesting that there may be a genetic influence in their development, although social learning remains an important factor [64,65]. Whilst several candidate genes have been proposed as being linked to FGIDs, no study to date has identified a single gene locus, although it must be noted that several of the published studies are small and statistically under powered to detect what is probably a small influence. Over the recent past the genome wide association studies have been a fruitful line of enquiry for delineating the genetic factors that contribute to the development of other GI disorders [66,67]. However, it is our opinion that such methodologies currently have limited applicability within FGIDs, as the prerequisite step for their success remains the further definition of the clinical phenotype based on pathophysiological features rather than purely symptom based criteria.

4.7.2. The stress responsive systems – the autonomic nervous system and the hypothalamic pituitary adrenal axis

Stress may be defined as an acute threat to homeostasis engendering an adaptive, or if chronic, a potentially maladaptive response. The response to stress in the GI tract is co-ordinated within the brain gut axis by the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis [68].

Central communication to the GI tract is via the parasympathetic and sympathetic pathways of the efferent ANS. Autonomic dysfunction has been demonstrated in a number of syndromes where chronic pain is a feature, such as IBS, fibromyalgia and chronic pelvic pain [69,70]. To date, specific patterns of dysautonomia have not been consistently demonstrated largely due to the heterogeneity of FGIDs, lack of control for psychological factors and the multiple differences in methodologies employed for recording and analysing autonomic data. In a recent systematic review, Masurak et al. reported that most studies reported no difference in autonomic measures when comparing IBS patients to healthy controls. However, when following sub-classification of IBS sufferers according to their predominant bowel habit, those with constipation had decreased parasympathetic and increased sympathetic tone in comparison to those with diarrhoea predominant IBS [71]. However, such results must be tempered with a degree of caution, as we need to consider a number of important methodological considerations. For instance, whether autonomic parameters derived from the measurement of heart rate variability is a sufficiently sensitive surrogate marker of specific gut autonomic innervation is uncertain. Moreover, with many measures of autonomic tone that are currently and widely utilized, there are considerable limitations regarding their temporal resolution. However, Keszthelyi et al. note in a recent review article "*new advances in* (autonomic neuroscience) *technology may give us the opportunity to expand on these experiments in a degree of detail not previously possible*" [72]. Our group and others have recently started using such a novel piece of technology, known as the Neuroscope, which allows the real time beat-to-beat measurement of validated markers of PNS tone. This measure has begun to provide fascinating insights into autonomic responses to mechanical and acid induced oesophageal pain [73–75].

Similarly, the HPA axis exerts important influences on immune function, motility and sensation within the GI tract [76,77]. Dysfunction of the HPA axis has been recognized in a number of chronic pain syndromes [78]. In a recent study of patients with non-cardiac chest pain, it was found that patients had elevated cortisol at baseline and following the administration of somatic and visceral pain in comparison to healthy controls [79]. Similarly in a study by Dinan et al., the HPA axis was examined in a group of 76 IBS patients and 75 healthy controls. It was found that in the IBS group, irrespective of IBS sub-type as defined by predominant stool consistency, there was over activity of the HPA axis and an excess of the pro-inflammatory cytokines interleukin 6 and 8 [80].

4.8. Associated and emerging mechanisms in chronic visceral pain syndromes

4.8.1. Gastrointestinal microbiota

The human microbiota is a diverse and dynamic ecosystem, which has evolved to form a symbiotic relationship with the host. The microbiota safeguards the host from external pathogens, aids in the metabolism of polysaccharides and lipids, modulates intestinal motility, in addition to modulating visceral perception [81]. There is a gradual increase in the concentration of microbiota along the GI tract, peaking at 10^{10-12} colony forming units per gram of

faeces in the colon, which is composed of between 400 and 1000 different species [82]. *Bacteroides* and *Firmicutes* are the two predominant bacterial phylotypes, with *Proteobacteria*, *Actinobacteria*, *Fusobacteria* and *Verrucomicrobia* phyla present in relatively low concentrations [83]. Several lines of evidence indicate that bacteria may be involved in the pathogenesis and pathophysiology of many FGIDs, via the metabolic capacity of luminal microbiota, and the potential of the mucosa associated microbiota to influence the host via immune–microbial interactions [84]. For instance, in addition to the phenomenon of PI-IBS, there are studies reporting a beneficial effect of interventions directed at altering the GI microbiota [85]. The relevance of small intestinal bacterial overgrowth in IBS remains to be fully determined, on account of methodological problems, the influence of confounding factors and multiple large differences between reported studies [86]. A recent important study by Jeffery et al. performed a detailed pyrosequencing analysis of faecal microbiota composition and demonstrated two species specific subtypes of IBS, independent of symptom based classification derived from the Rome III criteria [87]. The first of these showed a microbial composition similar to normal whereas the second was characterized by an increase in *Firmicutes*-associated taxa in association with a relative depletion of *Bacteroides*-related taxa. The implication of these data is that in future GI microbial enterotyping may facilitate stratifications of IBS sub-populations. However, at the present time such methods have limited practicality as a routine clinical biomarker as they are resource and labour intensive [88]. Nevertheless, there is intense commercial interest in the GI microbiota reflected in the expanding market of probiotics and prebiotics, some of which have shown benefits in the setting of clinical trials [89].

4.8.2. Narcotic bowel syndrome

Opioids markedly influence GI motility and such effects may manifest as constipation, nausea and bloating [90]. Although opioid analgesics can relieve pain effectively, the side effects of chronic opioid administration often limit their therapeutic benefit. For instance, constipation is known to occur in 15–90% on patients receiving opioids and have a negative impact on quality of life [91]. Counter-intuitively, abdominal pain can be a side effect of chronic opioids therapy and when it becomes the predominant side effect, it is known as narcotic bowel syndrome. Paradoxically, there is an increase in abdominal pain despite continued or escalating dosing of opioids by the clinician in an attempt to relieve the abdominal pain. Narcotic bowel syndrome is characterized by chronic or intermittent colicky abdominal pain or discomfort that worsens after the analgesic effects of opioids wear off. Escalating the opioid dosage only compounds the effect on pain sensitivity and further reduces GI secretion and motility. However, given the profound analgesic effects of opioids it is somewhat baffling to accept the argument that opioids can provoke the very pain that they are treating. Evidence from a number of recently published studies has shown that pain may be dynamically modulated by the CNS, peripheral neural and opioid pathways which inhibit, as well as facilitate, pain perception [90]. Moreover, chronic opioid use induces neuroplastic changes that paradoxically enhance hyperalgesia and give rise to tolerance. It has been proposed that there are at least 3 putative mechanisms that may lead to pro-nociceptive opioid effects: bimodal opioid dysregulation, abnormalities in counter-regulatory mechanisms and glial activation, see reviews by Grunkemaier et al. and Farmer et al. [90,92].

4.8.3. Connective tissue disorders

Within current gastroenterological practice, many patients in our opinion with unexplained GI symptoms are often erroneously classified as having a FGID, despite clinical features being evident of the presence of a more widespread systemic disorder. Data from our group and others have suggested that symptoms that would traditionally been considered to be typical of FGIDs may in fact be GI manifestations of hereditary disorders of connective tissue, the most prevalent example being joint hypermobility syndrome (JHS), a disorder many authorities consider to be indistinguishable from Ehlers–Danlos syndrome hypermobility-type [93,94]. JHS is characterized by musculoskeletal symptoms in a hypermobile individual in the absence of a systemic rheumatological disease. JHS and FGIDs share many epidemiological and extra-GI features [95]. Studies have linked JHS with a number of GI symptoms such as abdominal pain, nausea, bloating, constipation and diarrhoea [93] as well as abnormalities in GI physiology [96]. The rationale for linking these two seemingly dissimilar entities centres around the abnormalities in the extracellular connective tissue matrix. Such abnormalities maybe readily identifiable in the musculoskeletal system as excessive joint mobility, yet to date scant attention has been placed on assessing for such pathology within the GI tract. The sensorimotor apparatus of the GI tract is embedded within connective tissue which itself significantly contributes to the biomechanical properties of the viscera. Changes in the rate or degree of deformation/stretch in the GI tract are likely to influence the function of cellular mechano-receptors such as intramuscular arrays, intra-ganglionic laminar endings and interstitial cells of Cajal. Considering that acquired medical conditions that alter the structure and function of the extracellular matrix of the GI tract, such as systemic sclerosis, are characterized by reduced compliance and ineffective GI motility, it is not unreasonable to propose that similar abnormalities exist in JHS. Nevertheless, these putative associations warrant further investigation in a well-designed longitudinal epidemiological study.

4.8.4. Gastrointestinal neuromuscular disease

The term GI neuromuscular diseases refer to a heterogeneous group of disorders in which symptoms arise from impaired GI motor activity often manifesting as abnormal transit with or without radiological evidence of transient or persistent dilation of the viscera. Primary causes refer to disorders limited to the GI tract and secondary to those that are part of a systemic condition. Potentially, all segments of the GI tract can be affected from the oesophagus to the rectum. Whilst a number of disorders maybe readily identified, such as achalasia or Hirschsprung's disease, the cause in a number of patients are not. However, there are numerous small case series reported in the literature that have associated gastrointestinal neuromuscular diseases with a number of underlying histopathological abnormalities. Nevertheless, the diagnosis of GI neuromuscular disease has been hampered by inadequate morphological study and lack of standardization in histological reporting of the different components of the enteric neuromusculature. These deficiencies have recently been addressed by an international working group who have provided a comprehensive structured system of classification accompanied by robust diagnostic criteria [97]. This initiative particularly highlights the utility of taking a full thickness sample of GI tissue in facilitating a diagnosis [98]. Such pathophysiological stratifications may lead to improvements in treatment strategies, which in future can potentially be mechanism based, rather than being focused on symptom relief and palliation.

4.9. A new way forward on the road to the Fourth Rome consensus on functional gastrointestinal disorders? The emerging concept of pain clusters

The Rome diagnostic criteria for FGIDs, whose process employs a consensus approach which critically appraises the available evidence, is shortly to undergo its fourth iteration. These diagnostic criteria are based on characteristic symptoms within a

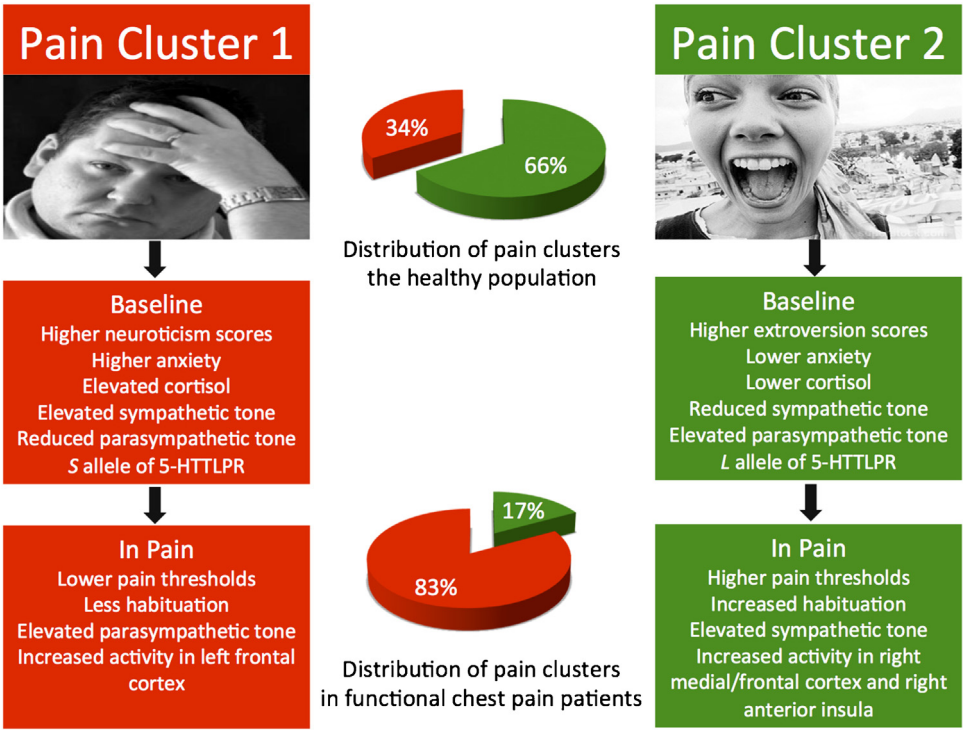

Fig. 4. A schematic representation of the pain clusters and their relative distributions in health and in patients with functional chest pain.

defined temporal pattern. Whilst this process has unarguably enhanced homogeneity with the research niche, it has not always translated to improvements in patient satisfaction and outcomes [99]. Although the sub-typing of disorders, such as IBS based on predominant symptom pattern such as diarrhoea or constipation, has improved the stratification of treatment interventions, to many experts it remains a source of controversy. Considering that visceral pain is a common defining feature of FGIDs, its experience is subject to marked inter-individual variability. This variability is multiply determined through genetic, psychological, physiological and neuroanatomical factors [100]. Whilst numerous studies have identified and examined many of these factors in isolation, such a singular approach has constrained our wider understanding of their co-relationships within possible homogenous sub-groups or "pain clusters." The development of homogeneous sub-groups for human disease susceptibilities has received considerable attention in other disciplines such as psychiatry [101]. There is a corresponding need for such an approach within FGIDs, as contemporaneous studies are fraught with difficulties in identifying homogenous groups of participants both in health and in FGIDs [102–104]. In a recent study, we have attempted to define distinct pain clusters comprising of differing personality traits, stress responsive physiology and genetic profiles coupled with differences in brain processing of somatic and visceral pain. We demonstrated the existence of two temporally stable pain clusters in health. The first of these, accounting for approximately 1/3rd of healthy subjects, had higher neuroticism/anxiety scores, sympathetic tone and cortisol levels at baseline yet during pain, they had lower pain tolerance thresholds and increased their parasympathetic tone. In this pain cluster, the serotonin transporter long polymorphic region (5HTTLPR) short allele was over-represented. The second pain cluster, accounting for approximately 2/3rds of healthy subjects, had the converse profile at baseline and during pain. Brain activity differed between the two clusters, with the first cluster having greater activity in left frontal cortex, whereas the second showed greater activity in the right medial/frontal cortex and right anterior insula (see Fig. 4). In a follow on study, we have evaluated these pain clusters in a preliminary cohort of patients with functional chest of presumed oesophageal origin, a diagnosis akin to that of non-cardiac chest pain. We found that patients were over-represented in pain cluster 1 (relative risk 3.6, 95% confidence interval 1.3–10.5, $p = 0.004$)[79]. In future it may be possible that such psychophysiological characterizations may aid in the identification of subjects at risk for developing chronic pain syndromes, such as FGID, and reduce variability in brain imaging and genetic studies. Furthermore, when applied to FGID it may allow stratification of patients and "personalization" of therapeutic interventions as the two clusters may differentially respond. The adoption of such a strategy may refine in diagnostic criteria and management, a key consideration in over burden healthcare economies, and ultimately improve patient outcomes. Assimilating the evidence that we have discussed in this paper, it is likely that FGID as an overall entity represent a heterogenous group of disorders which encompasses structural, inflammatory and biochemical abnormalities. Moreover, within the contemporaneous diagnostic criteria, such abnormalities maybe variable present even within a singular diagnostic group. For example certain patients with IBS may have a largely structural abnormality whereas in others inflammation may predominant. Perhaps we need to move away from the label of functional bowel disorders as in the coming decades it will be possible to identify predominant mechanisms of disease in individual patients.

5. Conclusions and implications

Important advances in our understanding of mechanisms that underlie both the development and maintenance of visceral pain have been achieved through convergent research strategies across a diverse array of academic disciplines encompassing neurogastroenterology, molecular pharmacology, neurophysiology and psychology. Nevertheless further challenges remain if we are to provide evidence based efficacious treatments to our patients with chronic visceral pain syndromes.

Conflict of interest statement

None of the authors have any conflict of interests to declare.

References

[1] Drossman DA. Rome III: the functional gastrointestinal disorders. McLean, VA: Degnon Associates; 2006.
[2] Leadley RM, Armstrong N, Lee YC, Allen A, Kleijnen J. Chronic diseases in the European Union: the prevalence and health cost implications of chronic pain. J Pain Palliat Care Pharmacother 2012;26:310–25.
[3] European Federation of IASP chapters. European Year Against Pain 2012 – Visceral Pain. http://www.efic.org/index.asp?sub=F8AMLHLAP9216P&topicsid=256 [accessed 14.12.13].
[4] Holschneider DP, Bradesi S, Mayer EA. The role of experimental models in developing new treatments for irritable bowel syndrome. Expert Rev Gastroenterol Hepatol 2011;5:43–57.
[5] Sikandar S, Dickenson AH. Visceral pain: the ins and outs, the ups and downs. Curr Opin Support Palliat Care 2012;6:17–26.
[6] Blackshaw LA, Gebhart GF. The pharmacology of gastrointestinal nociceptive pathways. Curr Opin Pharmacol 2002;2:642–9.
[7] Blackshaw LA, Brierley SM, Hughes PA, Harrington AM. The hot mustard receptor's role in gut motor function. Gastroenterology 2011;141:423–7.
[8] Aziz Q, Botha C, Willert R. Pharmacology of visceral pain: central factors. Dig Dis 2009;27(Suppl. 1):31–41.
[9] Anand P, Aziz Q, Willert R, van Oudenhove L. Peripheral and central mechanisms of visceral sensitization in man. Neurogastroenterol Motil 2007;19:29–46.
[10] Knowles CH, Aziz Q. Basic and clinical aspects of gastrointestinal pain. Pain 2009;141:191–209.
[11] Tillisch K, Mayer EA. Pain perception in irritable bowel syndrome. CNS Spectr 2005;10:877–82.
[12] Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. Gastroenterology 2011;140:91–100.
[13] Corazziari E. Definition and epidemiology of functional gastrointestinal disorders. Best Pract Res Clin Gastroenterol 2004;18:613–31.
[14] Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. Aliment Pharmacol Ther 2003;17:643–50.
[15] Saito YA, Talley NJL, Fett JM, Zinsmeister S, Locke ARGR. The effect of new diagnostic criteria for irritable bowel syndrome on community prevalence estimates. Neurogastroenterol Motil 2003;15:687–94.
[16] Drossman DA, Li Z, Andruzzi E, Temple RD, Talley NJ, Thompson WG, Whitehead WE, Janssens J, Funch-Jensen P, Corazziari E, Richter JE. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. Dig Dis Sci 1993;38:1569–80.
[17] Yu S, Ouyang A. TRPA1 in bradykinin-induced mechano-hypersensitivity of vagal C fibers in guinea pig esophagus. Am J Physiol Gastrointest Liver Physiol 2009;296:G255–65.
[18] Jones III RC, Xu L, Gebhart GF. The mechanosensitivity of mouse colon afferent fibers and their sensitization by inflammatory mediators require transient receptor potential vanilloid 1 and acid-sensing ion channel 3. J Neurosci 2005;25:10981–9.
[19] Knowles CH, Aziz Q. Visceral hypersensitivity in non-erosive reflux disease. Gut 2008;57:674–83.
[20] Winston J, Shenoy M, Medley D, Naniwadekar A, Pasricha PJ. The vanilloid receptor initiates and maintains colonic hypersensitivity induced by neonatal colon irritation in rats. Gastroenterology 2007;132:615–27.
[21] Levine JD, Alessandri-Haber N. TRP channels: targets for the relief of pain. Biochim Biophys Acta 2007;1772:989–1003.
[22] Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997;389:816–24.
[23] Holzer P. TRPV1 and the gut: from a tasty receptor for a painful vanilloid to a key player in hyperalgesia. Eur J Pharmacol 2004;500:231–41.
[24] Akbar A, Walters JR, Ghosh S. Review article: visceral hypersensitivity in irritable bowel syndrome: molecular mechanisms and therapeutic agents. Aliment Pharmacol Ther 2009;30:423–35.
[25] Banerjee B, Medda BK, Lazarova Z, Bansal N, Shaker R, Sengupta JN. Effect of reflux-induced inflammation on transient receptor potential vanilloid one (TRPV1) expression in primary sensory neurons innervating the oesophagus of rats. Neurogastroenterol Motil 2007;19:681–91.
[26] Akbar A, Yiangou Y, Facer P, Walters JR, Anand P, Ghosh S. Increased capsaicin receptor TRPV1-expressing sensory fibres in irritable bowel syndrome and their correlation with abdominal pain. Gut 2008;57:923–9.
[27] Gomes RB, Brodskyn C, de Oliveira CI, Costa J, Miranda JC, Caldas A, Valenzuela JG, Barral-Netto M, Barral A. Seroconversion against Lutzomyia longipalpis saliva concurrent with the development of anti-Leishmania chagasi delayed-type hypersensitivity. J Infect Dis 2002;186:1530–4.
[28] Othman AA, Nothaft W, Awni WM, Dutta S. Pharmacokinetics of the TRPV1 antagonist ABT-102 in healthy human volunteers: population analysis of data from 3 phase 1 trials. J Clin Pharmacol 2012;52:1028–41.
[29] Krarup AL, Ny L, Astrand M, Bajor A, Hvid-Jensen F, Hansen MB, Simren M, Funch-Jensen P, Drewes AM. Randomised clinical trial: the efficacy of a transient receptor potential vanilloid 1 antagonist AZD1386 in human oesophageal pain. Aliment Pharmacol Ther 2011;33:1113–22.
[30] Quiding H, Jonzon B, Svensson O, Webster L, Reimfelt A, Karin A, Karlsten R, Segerdahl M. TRPV1 antagonistic analgesic effect: a randomized study of AZD1386 in pain after third molar extraction. Pain 2013;154:808–12.
[31] Vergnolle N. Modulation of visceral pain and inflammation by protease-activated receptors. Br J Pharmacol 2004;141:1264–74.
[32] Vergnolle N, Wallace JL, Bunnett NW, Hollenberg MD. Protease-activated receptors in inflammation, neuronal signaling and pain. Trends Pharmacol Sci 2001;22:146–52.
[33] Landis RC. Protease activated receptors: clinical relevance to hemostasis and inflammation. Hematol Oncol Clin North Am 2007;21:103–13.
[34] Vergnolle N. Postinflammatory visceral sensitivity and pain mechanisms. Neurogastroenterol Motil 2008;20(Suppl. 1):73–80.
[35] Asfaha S, Cenac N, Houle S, Altier C, Papez MD, Nguyen C, Steinhoff M, Chapman K, Zamponi GW, Vergnolle N. Protease-activated receptor-4: a novel mechanism of inflammatory pain modulation. Br J Pharmacol 2007;150:176–85.
[36] Sarkar S, Aziz Q, Woolf CJ, Hobson AR, Thompson DG. Contribution of central sensitisation to the development of non-cardiac chest pain. Lancet 2000;356:1154–9.
[37] Sarkar S, Hobson AR, Hughes A, Growcott J, Woolf CJ, Thompson DG, Aziz Q. The prostaglandin E2 receptor-1 (EP-1) mediates acid-induced visceral pain hypersensitivity in humans. Gastroenterology 2003;124:18–25.
[38] Grundy D, Al-Chaer ED, Aziz Q, Collins SM, Ke M, Tache Y, Wood JD. Fundamentals of neurogastroenterology: basic science. Gastroenterology 2006;130:1391–411.
[39] Willert RP, Woolf CJ, Hobson AR, Delaney C, Thompson DG, Aziz Q. The development and maintenance of human visceral pain hypersensitivity is dependent on the N-methyl-D-aspartate receptor. Gastroenterology 2004;126:683–92.
[40] Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable colon syndrome. Gut 1973;14:125–32.
[41] Whitehead WE, Holtkotter B, Enck P, Hoelzl R, Holmes KD, Anthony J, Shabsin HS, Schuster MM. Tolerance for rectosigmoid distention in irritable bowel syndrome. Gastroenterology 1990;98:1187–92.
[42] Mertz H, Naliboff B, Munakata J, Niazi N, Mayer EA. Altered rectal perception is a biological marker of patients with irritable bowel syndrome. Gastroenterology 1995;109:40–52.
[43] Lemann M, Dederding JP, Flourie B, Franchisseur C, Rambaud JC, Jian R. Abnormal perception of visceral pain in response to gastric distension in chronic idiopathic dyspepsia. The irritable stomach syndrome. Dig Dis Sci 1991;36:1249–54.
[44] Cook IJ, van Eeden A, Collins SM. Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. Gastroenterology 1987;93:727–33.
[45] Verne GN, Himes NC, Robinson ME, Gopinath KS, Briggs RW, Crosson B, Price DD. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. Pain 2003;103:99–110.
[46] Bouin M, Meunier P, Riberdy-Poitras M, Poitras P. Pain hypersensitivity in patients with functional gastrointestinal disorders: a gastrointestinal-specific defect or a general systemic condition? Dig Dis Sci 2001;46:2542–8.
[47] Whitehead WE, Engel BT, Schuster MM. Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. Dig Dis Sci 1980;25:404–13.
[48] Nasr I, Attaluri A, Coss-Adame E, Rao SS. Diagnostic utility of the oesophageal balloon distension test in the evaluation of oesophageal chest pain. Aliment Pharmacol Ther 2012;35:1474–81.
[49] Neal KR, Barker L, Spiller RC. Prognosis in post-infective irritable bowel syndrome: a six year follow up study. Gut 2002;51:410–3.
[50] Ghoshal UC, Ranjan P. Post-infectious irritable bowel syndrome: the past, the present and the future. J Gastroenterol Hepatol 2011;26(Suppl. 3):94–101.
[51] Garg AX, Macnab J, Clark W, Ray JG, Marshall JK, Suri RS, Devereaux PJ, Haynes B, Walkerton Health Study. Long-term health sequelae following *E. coli* and campylobacter contamination of municipal water. Population sampling and assessing non-participation biases. Can J Public Health 2005;96:125–30.
[52] Dunlop SP, Jenkins D, Neal KR, Spiller RC. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS. Gastroenterology 2003;125:1651–9.
[53] Han W, Wang Z, Lu X, Guo C. Protease activated receptor 4 status of mast cells in post infectious irritable bowel syndrome. Neurogastroenterol Motil 2012;24:113–9, e82.
[54] van Wanrooij SJ, Wouters MM, Van Oudenhove L, Vanbrabant W, Mondelaers S, Kollmann P, Kreutz F, Schemann M, Boeckxstaens GE. Sensitivity testing in irritable bowel syndrome with rectal capsaicin stimulations: role of TRPV1 upregulation and sensitization in visceral hypersensitivity? Am J Gastroenterol 2014;109:99–109.
[55] Wilder-Smith CH. The balancing act: endogenous modulation of pain in functional gastrointestinal disorders. Gut 2011;60:1589–99.
[56] Mikocka-Walus A, Turnbull D, Moulding N, Wilson I, Andrews JM, Holtmann G. Psychological comorbidity and complexity of gastrointestinal symptoms in clinically diagnosed irritable bowel syndrome patients. J Gastroenterol Hepatol 2008;23:1137–43.

[57] Spiller R, Aziz Q, Creed F, Emmanuel A, Houghton L, Hungin P, Jones R, Kumar D, Rubin G, Trudgill N, Whorwell P. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut 2007;56:1770–98.
[58] Tyler K, Moriceau S, Sullivan RM, Greenwood-van Meerveld B. Long-term colonic hypersensitivity in adult rats induced by neonatal unpredictable vs predictable shock. Neurogastroenterol Motil 2007;19:761–8.
[59] Elsenbruch S, Rosenberger C, Bingel U, Forsting M, Schedlowski M, Gizewski ER. Patients with irritable bowel syndrome have altered emotional modulation of neural responses to visceral stimuli. Gastroenterology 2010;139:1310–9.
[60] Leserman J, Drossman DA. Relationship of abuse history to functional gastrointestinal disorders and symptoms: some possible mediating mechanisms. Trauma Violence Abuse 2007;8:331–43.
[61] Barreau F, Ferrier L, Fioramonti J, Bueno L. New insights in the etiology and pathophysiology of irritable bowel syndrome: contribution of neonatal stress models. Pediatr Res 2007;62:240–5.
[62] Alander T, Heimer G, Svardsudd K, Agreus L. Abuse in women and men with and without functional gastrointestinal disorders. Dig Dis Sci 2008;53:1856–64.
[63] Gwee KA, Graham JC, McKendrick MW, Collins SM, Marshall JS, Walters SJ, Read NW. Psychometric scores and persistence of irritable bowel after infectious diarrhoea. Lancet 1996;347:150–3.
[64] Saito YA, Zimmerman JM, Harmsen WS, De Andrade M, Locke 3rd GR, Petersen GM, Talley NJ. Irritable bowel syndrome aggregates strongly in families: a family-based case–control study. Neurogastroenterol Motil 2008;20:790–7.
[65] Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Gastroenterology 2001;121:799–804.
[66] Rioux JD, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A, Green T, Kuballa P, Barmada MM, Datta LW, Shugart YY, Griffiths AM, Targan SR, Ippoliti AF, Bernard EJ, Mei L, Nicolae DL, Regueiro M, Schumm LP, Steinhart AH, Rotter JI, Duerr RH, Cho JH, Daly MJ, Brant SR. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. Nat Genet 2007;39:596–604.
[67] Mells GF, Floyd JA, Morley KI, Cordell HJ, Franklin CS, Shin SY, Heneghan MA, Neuberger JM, Donaldson PT, Day DB, Ducker SJ, Muriithi AW, Wheater EF, Hammond CJ, Dawwas MF, UP Consortium, Wellcome Trust Case Control Consortium, Jones DE, Peltonen L, Alexander GJ, Sandford RN, Anderson CA. Genome-wide association study identifies 12 new susceptibility loci for primary biliary cirrhosis. Nat Genet 2011;43:329–32.
[68] Jones MP, Dilley JB, Drossman D, Crowell MD. Brain–gut connections in functional GI disorders: anatomic and physiologic relationships. Neurogastroenterol Motil 2006;18:91–103.
[69] Tillisch K, Mayer EA, Labus JS, Stains J, Chang L, Naliboff BD. Sex specific alterations in autonomic function among patients with irritable bowel syndrome. Gut 2005;54:1396–401.
[70] Staud R, Rodriguez ME. Mechanisms of disease: pain in fibromyalgia syndrome. Nat Clin Pract Rheumatol 2006;2:90–8.
[71] Mazurak N, Seredyuk N, Sauer H, Teufel M, Enck P. Heart rate variability in the irritable bowel syndrome: a review of the literature. Neurogastroenterol Motil 2012;24:206–16.
[72] Keszthelyi D, Troost FJ, Masclee AA. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. Methods to assess visceral hypersensitivity in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 2012;303:G141–54.
[73] Chua YC, Ng KS, Sharma A, Jafari J, Surguy S, Yazaki E, Knowles CH, Aziz Q. Randomised clinical trial: pregabalin attenuates the development of acid-induced oesophageal hypersensitivity in healthy volunteers – a placebo-controlled study. Aliment Pharmacol Ther 2012;35:319–26.
[74] Sharma A, Paine P, Rhodes S, Warburton F, Chua YC, Aziz Q. The autonomic response to human esophageal acidification and the development of hyperalgesia. Neurogastroenterol Motil 2012;24:e285–93.
[75] Paine P, Kishor J, Worthen SF, Gregory LJ, Aziz Q. Exploring relationships for visceral and somatic pain with autonomic control and personality. Pain 2009;144:236–44.
[76] Ohman L, Simren M. New insights into the pathogenesis and pathophysiology of irritable bowel syndrome. Dig Liver Dis 2007;39:201–15.
[77] Drossman DA. What does the future hold for irritable bowel syndrome and the functional gastrointestinal disorders? J Clin Gastroenterol 2005;39: S251–6.
[78] Wingenfeld K, Heim C, Schmidt I, Wagner D, Meinlschmidt G, Hellhammer DH. HPA axis reactivity and lymphocyte glucocorticoid sensitivity in fibromyalgia syndrome and chronic pelvic pain. Psychosom Med 2008;70:65–72.
[79] Farmer AD, Kano M, Coen SJ, Navqi H, Furlong PL, Scott SM, Knowles CH, Lightman S, Aziz Q. Psychophysiological responses to oesophageal stimulation in functional chest pain: a case control study. Neurogastroenterol Motil 2014;26:139–48.
[80] Dinan TG, Quigley EM, Ahmed SM, Scully P, O'Brien S, O'Mahony L, O'Mahony S, Shanahan F, Keeling PW. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? Gastroenterology 2006;130:304–11.
[81] Montiel-Castro AJ, Gonzalez-Cervantes RM, Bravo-Ruiseco G, Pacheco-Lopez G. The microbiota–gut–brain axis: neurobehavioral correlates, health and sociality. Front Integr Neurosci 2013;7:70.
[82] Bercik P. The microbiota–gut–brain axis: learning from intestinal bacteria? Gut 2011;60:288–9.
[83] Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. Science 2005;308:1635–8.
[84] Salonen A, de Vos WM, Palva A. Gastrointestinal microbiota in irritable bowel syndrome: present state and perspectives. Microbiology 2010;156:3205–15.
[85] Pimentel M, Lembo A, Chey WD, Zakko S, Ringel Y, Yu J, Mareya SM, Shaw AL, Bortey E, Forbes WP, Group TS. Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22–32.
[86] Simren M, Barbara G, Flint HJ, Spiegel BM, Spiller RC, Vanner S, Verdu EF, Whorwell PJ, Zoetendal EG, Rome Foundation C. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut 2013;62:159–76.
[87] Jeffery IB, O'Toole PW, Ohman L, Claesson MJ, Deane J, Quigley EM, Simren M. An irritable bowel syndrome subtype defined by species-specific alterations in faecal microbiota. Gut 2012;61:997–1006.
[88] Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, de Vos WM, Brunak S, Dore J, Meta HITC, Antolin M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Merieux A, Melo Minardi R, M'Rini C, Muller J, Oozeer R, Parkhill J, Renault P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. Nature 2011;473:174–80.
[89] Aziz Q, Dore J, Emmanuel A, Guarner F, Quigley EM. Gut microbiota and gastrointestinal health: current concepts and future directions. Neurogastroenterol Motil 2013;25:4–15.
[90] Grunkemeier DM, Cassara JE, Dalton CB, Drossman DA. The narcotic bowel syndrome: clinical features, pathophysiology, and management. Clin Gastroenterol Hepatol 2007;5:1126–39, quiz 1-2.
[91] Davis MP. The opioid bowel syndrome: a review of pathophysiology and treatment. J Opioid Manag 2005;1:153–61.
[92] Farmer AD, Ferdinand E, Aziz Q. Opioids and the gastrointestinal tract – a case of narcotic bowel syndrome and literature review. J Neurogastroenterol Motil 2013;19:94–8.
[93] Zarate N, Farmer AD, Grahame R, Mohammed SD, Knowles CH, Scott SM, Aziz Q. Unexplained gastrointestinal symptoms and joint hypermobility: is connective tissue the missing link? Neurogastroenterol Motil 2010;22:252–78.
[94] Zeitoun JD, Lefevre JH, de Parades V, Sejourne C, Sobhani I, Coffin B, Hamonet C. Functional digestive symptoms and quality of life in patients with Ehlers–Danlos syndromes: results of a national cohort study on 134 patients. PLoS ONE 2013;8:e80321.
[95] Hakim A, Keer R, Grahame R. Hypermobility, fibromyalgia and chronic pain. Edinburgh: Churchill Livingstone; 2010.
[96] Mohammed SD, Lunniss PJ, Zarate N, Farmer AD, Grahame R, Aziz Q, Scott SM. Joint hypermobility and rectal evacuatory dysfunction: an etiological link in abnormal connective tissue? Neurogastroenterol Motil 2010;22:1085–283.
[97] Knowles CH, De Giorgio R, Kapur RP, Bruder E, Farrugia G, Geboes K, Gershon MD, Hutson J, Lindberg G, Martin JE, Meier-Ruge WA, Milla PJ, Smith VV, Vandervinden JM, Veress B, Wedel T. Gastrointestinal neuromuscular pathology: guidelines for histological techniques and reporting on behalf of the Gastro 2009 International Working Group. Acta Neuropathol 2009;118:271–301.
[98] Knowles CH, De Giorgio R, Kapur RP, Bruder E, Farrugia G, Geboes K, Lindberg G, Martin JE, Meier-Ruge WA, Milla PJ, Smith VV, Vandervinden JM, Veress B, Wedel T. The London Classification of gastrointestinal neuromuscular pathology: report on behalf of the Gastro 2009 International Working Group. Gut 2010;59:882–7.
[99] Corsetti M, Tack J. FDA and EMA end points: which outcome end points should we use in clinical trials in patients with irritable bowel syndrome? Neurogastroenterol Motil 2013;25:453–7.
[100] Edwards RR. Individual differences in endogenous pain modulation as a risk factor for chronic pain. Neurology 2005;65:437–43.
[101] Robbins TW, Gillan CM, Smith DG, de Wit S, Ersche KD. Neurocognitive endophenotypes of impulsivity and compulsivity: towards dimensional psychiatry. Trends Cogn Sci 2012;16:81–91.
[102] Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003;160:636–45.
[103] Tracey I. Can neuroimaging studies identify pain endophenotypes in humans? Nat Rev Neurol 2011;7:173–81.
[104] Mayer EA, Aziz Q, Coen S, Kern M, Labus JS, Lane R, Kuo B, Naliboff B, Tracey I. Brain imaging approaches to the study of functional GI disorders: a Rome working team report. Neurogastroenterol Motil 2009;21:579–96.