Central nervous system involvement in functional gastrointestinal disorders

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Although functional gastrointestinal disorders (FGID) are common, their pathophysiology remains incompletely understood. It is generally accepted that dysfunction of the bidirectional pathways between the gastrointestinal tract and the central nervous system (the ‘brain–gut axis’) at any level can cause FGID symptoms. In this review article, we focus on the role of the central nervous system in the brain—gut axis.

First, we describe the functional anatomy of the brain—gut axis. Second, we focus on the results from brain-imaging studies both in healthy volunteers and in FGID patients. These new investigational techniques made identification of brain regions critically involved in processing of visceral afferent information possible. Differences in central nervous system response to visceral stimuli between controls and FGID patients will be highlighted. Third, we will address the issue of high comorbidity with psychiatric disorders. Some hypotheses about common pathophysiological substrates will be discussed.

Key words: functional gastrointestinal disorders; brain—gut axis; visceral; pain; psychiatric disorders; brain imaging.
Functional disorders of the gastrointestinal tract (FGID) are common and often chronic, disabling conditions accounting for a substantial percentage of primary care as well as gastroenterology specialist visits. Well-designed epidemiologic studies report prevalences in the community of up to 70%, depending among others on the diagnostic criteria used. Although only a relatively small percentage of the people affected seeks medical care, FGID account for as much as 40–60% of all outpatient gastroenterology clinic visits. Moreover, these frequent conditions are associated with significant work absenteeism, impaired health-related quality of life and high health-care utilization costs.

Classification of FGID is based on definitions (including symptom-based criteria) defined by an international group of experts during a consensus conference held in Rome ('The Rome Committee'). These definitions have recently been revised and updated during a second conference ('Rome II'). The pathophysiology of the disorders, however, remains incompletely understood. Originally, motor abnormalities of the gastrointestinal tract were considered to be the most important pathophysiological mechanism. Subsequently, attention shifted towards visceral hypersensitivity as the key pathogenetic factor underlying FGID. It has long been recognized that psychosocial factors have an important influence on both the onset and exacerbations of FGID, as well as on health-care seeking, illness behavior and therapeutic outcome. Moreover, comorbidity with psychiatric disorders is frequent. However, the exact mechanisms by which psychological disturbances (reflecting some kind of dysfunction of the central nervous system) may influence gut physiology—both motor and sensory—or the perception of visceral events remain until today largely unknown. Thanks to the development of new investigational techniques like functional Magnetic Resonance Imaging (fMRI), an increasing amount of research on the interaction between brain and gut has been conducted during the last few years. For example, the growing body of knowledge on the biological underpinnings of the stress response has provided more insight into the influence of stress, traditionally regarded as a ‘purely psychological’ phenomenon, on gut physiology and the perception of visceral events in health and disease. Furthermore, research using modern brain imaging techniques has shown a considerable overlap between regions involved in the processing of visceral sensation and regions important for emotional regulation, providing further support for the hypothesis that emotional state has an important influence on the function of the gastrointestinal tract and vice versa.

It is very likely that FGID—like most disease entities based on symptomatic rather than pathophysiologic criteria—are largely heterogeneous in nature. The etiology may be highly multifactorial and it is now widely accepted that dysfunction of the bidirectional neural pathways between the brain and the gut ('brain–gut axis', BGA) at any level can contribute to the various symptoms experienced by FGID patients. This model of bidirectional communication along the BGA provides a biological framework supporting a bio-psychosocial disease concept of FGID, integrating all the contributing factors, whether biological, psychological or social, and their reciprocal interactions. The relative contribution of the various factors may vary highly between different subgroups of patients and even within the same patient over time. For example, the abnormal perception of visceral pain (visceral hypersensitivity) can result from alterations in the physiology of peripheral sensory neurons innervating the gut, but also from abnormal processing or modulation of visceral sensory information at the level of the central nervous system (spinal cord or brain), or both. This last explanation may provide a neurobiological link between ‘psychological’ disturbances (for example anxiety, stress) and their neurobiological implications.
correlates at brain level on the one hand and gastrointestinal symptoms on the other hand.8,9,12,15–19

In this review article, we will focus mainly on the involvement of the central nervous system (CNS) part of the BGA in the pathophysiology of FGID. There is an increasing body of research on the mechanisms by which the CNS processes and/or modulates afferent information from the gastrointestinal tract, influences motor function of the gut and determines affective and behavioral responses to abnormal sensations. First, we will briefly address what is known about the normal anatomy and physiology of the BGA. Second, the results of recent studies using sophisticated techniques for examining the BGA in both health and disease will be reviewed, with special interest in the CNS. Third, we will provide an overview of the literature on comorbidity of FGID with psychiatric disorders, with special attention to common pathophysiological mechanisms at CNS level (including the biological correlates of stress) and their potential influence on BGA functioning.

FUNCTIONAL ANATOMY OF THE BRAIN–GUT AXIS (FIGURE 1)

Intrinsic innervation—enteric nervous system (ENS)

The ENS is structurally and functionally complex and is located within the wall of the gastrointestinal tract, sometimes named ‘mini-brain’ or ‘brain-in-the gut’ because it shares some important features with the CNS. For example, they have a common embryological origin and several neurotransmitters (serotonin or 5-hydroxytryptamine (5-HT), opiates, cholecystokinin (CCK), etc.) are found both in the brain and the gut wall.20 Under normal circumstances, the ENS automatically controls gut functions like motility, absorption and secretion, independent of the CNS. However, the CNS often modulates the functions of the ENS.5 Local events, like acute inflammation, can cause

![Functional neuroanatomy of the brain–gut axis.](image-url)
long-lasting or even permanent changes in the structure and function of the ENS. For example, inflammation can destroy ENS motor neurons, resulting in abnormal motility. This may provide a potential pathophysiological mechanism in (post-infectious) FGID. For a more extensive review of the structure and function of the ENS in both normal and pathological states, see reference 17.

Extrinsic innervation—autonomic nervous system (ANS)

Afferent pathways

Afferent pathways convey (sensory) information from the gastrointestinal tract to the CNS. Basically, there are two important and distinct afferent systems.

Vagal afferents

The vagus nerve innervates the whole gastrointestinal tract except the distal third of the colon. The cell bodies of the vagal afferent primary neurons lie in the ganglion nodosum, just below the foramen jugulare. They make synapse with secondary order neurons in the nucleus tractus solitarii (NTS), the main sensory nucleus of the vagus nerve. Most of these neurons send projections to the parabrachial nucleus (PBN) in the pons. From there on, fibers ascend to visceral sensory cortical areas (mainly the insular cortex (IC)) via the ventral posterior medial nucleus of the thalamus, but also directly to brain regions important for regulation of arousal, emotions and autonomic or behavioral responses like noradrenergic locus coeruleus (LC) and autonomic nuclei like the motor nucleus of the vagus nerve (these two are highly interconnected), hypothalamus, amygdala and anterior cingulate cortex (ACC). At lower levels, autonomic reflex loops take place. Moreover, stimulation of the LC may influence transmission of sensory information to higher brain centers and visceral motor responses, besides its well-known role in anxiety and arousal. At higher levels (IC, ACC), sensory information from the viscera is processed and integrated with information from other (exteroceptive and interoceptive) sensory modalities, long-term memory and information regarding emotional valence of intero- and exteroceptive stimuli in order to produce the most appropriate response.

Vagal afferents are saturated at low levels of stimulation, leading to the hypothesis that they mainly mediate physiological rather than harmful sensations.

Spinal visceral afferents

The cell bodies of the spinal afferent primary neurons lie in the dorsal root ganglia (DRG) and they make synapse at the level of the dorsal column of the spinal cord. From this level on, visceral sensory information is transmitted via a number of tracts within the spinal cord, like the dorsal columns, the medial and lateral spinothalamic tracts, among others.

The ‘lateral system’ consists of the lateral spinothalamic tract and its higher projections (ventroposterior thalamus and visceral sensory cortical areas like somatosensory cortices (S1, S2) and the IC). This system processes ‘sensory-discriminative’ aspects of pain (intensity, location, etc.).

The ‘medial system’, consisting of medial spinothalamic, spinoreticular, spinomesencephalic and spinohypothalamic tracts, on the contrary, mainly projects to relay stations in the brainstem or midbrain (reticular formation, NTS, periaqueductal gray (PAG), PBN). At this level, important projections to and interactions with arousal systems (reticular formation, LC, raphe nuclei), autonomic regions (hypothalamus, motor nucleus of the nervus vagus), descending antinociceptive centers (PAG)
and the fear system (amygdala) take place.\textsuperscript{9,23} From some of these relay stations on, third order neurons project to the medial and intralaminar nuclei of the thalamus. This part of the thalamus is sometimes called ‘the limbic thalamus’, because its neurons mainly project to areas involved in emotional functioning, like the ACC and the orbitomedial prefrontal cortex (PFC). This ‘medial system’ processes the ‘affective-motivational’ aspects of pain (suffering, unpleasantness, etc.).\textsuperscript{9}

Spinal visceral afferents are believed to transfer information about both physiological and noxious ranges of stimulation, including pain.\textsuperscript{8,9}

\textit{Sacral afferents}
Sacral afferents innervate the distal third of the colon. Their fibers follow pelvic nerves, cell bodies are located in the DRG.\textsuperscript{8}

\textit{Efferent pathways}
Efferent nerves modulate motor and secretory functions of the gut.\textsuperscript{8}

\textit{Vagal (parasympathetic) efferents}
The dorsal motor nucleus (DMN), located in the medulla, is the main motor nucleus of the vagus nerve. The fibers make synapse with ENS neurons within the gut wall, the main neurotransmitter involved is acetylcholine (Ach), with a stimulatory effect on GI motility.\textsuperscript{8} The DMN receives projections from the NTS, the LC, the hypothalamus, amygdala, IC and ACC,\textsuperscript{9,12,13} regions important for the regulation of arousal, fear, emotions and behavior.\textsuperscript{9,12,13}

\textit{Sacral (parasympathetic) efferents}
The distal third of the colon doesn’t receive parasympathetic innervation from the vagus nerve, but from preganglionic neurons originating in the intermediate grey matter at the spinal cord levels S1—S5. Postganglionic neurons lie in the pelvic ganglia, their fibers innervate the distal colon via pelvic nerves.\textsuperscript{8}

\textit{Splanchnic (sympathetic) efferents}
The cell bodies of the preganglionic (cholinergic) neurons are located in the intermediate grey matter of the thoracolumbar spinal cord, with synapses in the celiac, mesenteric and pelvic ganglia. From there on, postganglionic noradrenergic neurons project to the ENS neurons, with an inhibitory effect on gut motility.\textsuperscript{8} Like the parasympathetic preganglionic neurons, the sympathetic preganglionic neurons receive modulatory input from higher centers.\textsuperscript{8}

\textbf{CNS PROCESSING AND MODULATION OF PHYSIOLOGICAL AND NOXIOUS VISCERAL SENSATION}

Pain is the most commonly reported symptom in FGID and is often difficult to treat.\textsuperscript{4,7} Pain is a complex, highly subjective experience which involves many different components. This experience results from the interaction of three dimensions: a sensory-discriminative component (analysis of location, intensity and duration of the stimulus), an affective-motivational component (unpleasant character of pain experience, suffering) and finally a cognitive-evaluative component (anticipation, attention, integration with information from past experiences stored in long-term
memory, response selection). Those three dimensions highly influence each other. For example, it is well known that distraction of attention away from a pain stimulus has an important influence on subjective ratings of pain intensity (cognitive modulation). Moreover, recent research on visceral sensation indicates that the emotional context in which perception of oesophageal stimulation takes place modulates neural responses and subjective experience during this stimulation (emotional modulation). The affective-motivational component of pain experience consists of two subdivisions: the emotional feelings associated with the present or short-term future unpleasantness of pain on the one hand and the emotional feelings dealing with long-term implications of pain (‘secondary pain affect’) on the other hand. Furthermore, attention—itself part of the cognitive component—can be subdivided into non-specific arousal processes and more selective attentional or orientating processes. A recent study demonstrates that divided attention recruits more brain regions compared to selective attention.

It is believed that each of the three major dimensions arises from information processing in different but highly interacting brain circuits, which together constitute the CNS ‘pain matrix’, the neurobiological correlate of the subjective pain experience.

The ‘pain matrix’ in somatic pain

In a recent review and meta-analysis, Peyron et al summarize the evidence from brain imaging studies designed to examine the CNS response to acute somatic pain in normal volunteers. In summary, lateral thalamus, primary and secondary somatosensory cortices (S1, S2) and the IC are involved in the sensory-discriminative aspect of the pain experience, whereas activation of posterior parietal and prefrontal cortices (PFC) accounts for the cognitive-evaluative processing of painful somatic stimuli. Different subdivisions of the ACC may be important for cognitive and affective dimensions of the pain experience. This provides further support for the hypothesis that the ACC is a multi-integrative structure, consisting of several subdivisions which may have distinct functions not only in pain processing, but also more generally in cognitive and affective functioning. Finally, it should be noticed that in some studies, activation of the PAG was seen. This is a region involved in pain inhibition via descending inhibitory pathways (Figure 2).

CNS processing and modulation of visceral sensation and pain

There are some important differences between visceral and somatic sensation or pain. For example, visceral sensation is poorly localised and referral to other viscera or somatic regions is frequently seen. Although less studied than somatic pain, recent advances in understanding the CNS processing of visceral sensation and pain have been made, using functional neuroimaging techniques. The evidence has recently been reviewed by Derbyshire and Aziz et al. In summary, S2, IC, medial and orbital subdivisions of the PFC (MPFC, OPFC) and several subdivisions of the ACC are most consistently reported as being critical to CNS processing of visceral stimuli. S2 is important for primary processing of visceral sensation whereas higher processing may occur in the other regions.
The insular cortex

It is widely accepted that the IC is an important visceral sensorimotor area, receiving both somatic and visceral input from the sensory thalamus and the NTS, but also from the central nucleus of the amygdala and the rostral–ventral subdivision of the ACC, indicating that (visceral) sensory and emotional information are integrated in the anterior IC. Indeed, studies have shown that lesions in this region alter the emotional but not the sensory dimension of pain experiences. The main outputs from the IC go to autonomic nuclei (including the DMN), amygdala, OPFC & ACC, providing further evidence for the role of IC in autonomic & visceromotor function but also regulation of emotions.

The prefrontal cortex

Within the PFC, the OPFC and MPFC play a role in the regulation of visceral function (both sensory and motor) and mood. More in detail, the orbitofrontal network

Figure 2. Adapted from [23]. PAG, periaqueductal gray; PB, parabrachial nucleus of the dorsolateral pons; AMYG, amygdala; HT, hypothalamus; Vmpo, MDvc & VPL, thalamic nuclei (ventromedial part of the posterior nuclear complex, ventrocaudal part of the medial dorsal nucleus and ventroposterior lateral nucleus respectively); ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; PF, prefrontal cortex; SMA, supplementary motor area; S1 & S2, primary & secondary somatosensory cortices; M1, primary motor cortex; PPC, posterior parietal complex.
receives input from the different sensory modalities (visceral, visual, gustatory, etc.),
mostly related to feeding, as well as input from various areas involved in emotional
regulation (basal nucleus of the amygdala, hippocampus). Therefore, this may be a
region where integration of sensory and affective information takes place, in close
connection to the IC. The medial prefrontal network (partly overlapping with or
closely interconnected to the rostral–ventral subdivision of the ACC) mainly provides
output to brain regions involved in visceromotor, endocrine and behavioral responses
(autonomic nuclei, hypothalamus, PAG). The PAG may be ‘a center for coordination of
visceral and behavioral responses to stress or threatening stimuli’, including
antinociceptive responses through descending pathways terminating at the level of
the dorsal horn of the spinal cord. Similarly to the orbitofrontal network, the medial
prefrontal network has extensive reciprocal connections to the amygdala and other
regions involved in emotional regulation. In summary, these regions are important
for higher-order processing and integration of emotional and sensory information,
resulting in the choice of the most appropriate autonomous and behavioral response.

The dorsolateral subdivision of the PFC (DLPFC) is mainly involved in
cognitive functioning (attention, working memory, executive functions).

The anterior cingulate cortex (ACC)
The ACC is a complex, multi-integrative brain structure consisting of various sub-
divisions with distinct functions. There is a considerable amount of evidence
that ACC is involved in different dimensions of sensory and pain processing (emotional
dimension: encoding of pain unpleasantness; cognitive dimension: attention to sensory
information, etc.) as well as in various aspects of cognitive, motivational and emotional
functioning in general. As this brain region lies at the interface of sensory and
emotional processing, this may be one of the most important structures involved in
the influence of emotional state on perception of (visceral) sensation and/or pain, and vice
versa. Moreover, the ACC provides output to autonomic output structures
(autonomic nuclei, hypothalamus), regions involved in the regulation of arousal (LC)
and to the amygdala, suggesting that information processing by the ACC highly
influences autonomic responses and arousal (and vice versa).

Although it is generally accepted that the ACC consists of a number of distinct
specialized subdivisions which are part of different (but interconnected) networks or
‘processing modules’ for various kinds of information from different sources, it is far
less clear how exactly the ACC should be subdivided. Moreover, the terminology used to refer to different subregions is far from uniform.

We’ll mention some hypotheses briefly.

Based on a meta-analysis of brain-imaging studies of cognitive and emotional
tasks, Bush et al propose to divide the ACC into two distinct areas: a rostral–
ventral ‘affective’ subdivision (ACad) (Brodmann Areas (BA) 25 & 33 (ventral or
infragenual) and 24 & 32 (rostral or perigenual)) and a dorsal ‘cognitive’ division
(ACcd) (BA 24’ & 32’). This distinction seems not to be absolute and has not been
confirmed in all studies, possibly indicating that the two subdivisions closely interact
with each other. The ACad has reciprocal connections with several regions
involved in the regulation of emotions (amygdala, hippocampus, OPFC and with
autonomic, visceromotor and endocrine systems. Moreover, this region is involved
in emotional processing in normal subjects and is believed to be an important
substrate of mood and anxiety disorders.\textsuperscript{25,32--34} The ACcd, on the contrary, has strong reciprocal connections with areas known to be mainly involved in higher cognitive processes, like DLPFC, parietal cortex and supplementary motor area.\textsuperscript{25} Functions of this network include working memory, complex attention, anticipation and response selection.\textsuperscript{25}

Based on their meta-analysis of pain studies, Petrovic & Ingvar\textsuperscript{35} propose a slightly different way of subdividing the ACC. The first subdivision (‘caudal ACC’: posterior parts of BA 24 & 32, on the border with the posterior cingulate cortex (PCC, BA 23)) receives a lot of somatic and visceral nociceptive input and is activated by perception of pain per se. The main function attributed to the second subdivision (‘middle ACC’: anterior parts of BA 24 & 32, comparable to ACcd in the Bush hypothesis) is attention. The third subdivision (‘rostral ACC’: BA 24, 25, 32 & 33, comparable to ACad in the Bush hypothesis) is important for emotional processing, but has also been implicated in cognitive pain modulation. This region contains a lot of endogenous opioids and is believed to be, together with the amygdala, the major origin of descending antinociceptive pathways to the PAG.\textsuperscript{35} Moreover, a recent study shows a significant deactivation in \(\mu\)-opioid neurotransmission in the rostral subdivision of the ACC and in the amygdala during a sustained state of sadness in normal volunteers.\textsuperscript{36} In summary, the findings of Petrovic et al indicate that the distinction between affective and cognitive subdivisions within the ACC is not absolute, as the rostral subdivision may play a major role not only in emotional functioning per se, but also in processes reflecting interaction between cognition and emotion, like attention to emotionally significant stimuli.\textsuperscript{24,33,35}

Visceral hypersensitivity: a pathophysiological mechanism in FGID?

There is a growing amount of evidence that at least an important subgroup of FGID patients shows hypersensitivity to visceral stimuli, both at baseline and after repetitive stimulation of, for example, the rectosigmoid.\textsuperscript{2,4,6,7,9,10} This means that most FGID patients have significantly reduced thresholds to pain or discomfort in response to visceral stimulation. In other words, they will perceive a certain stimulus as uncomfortable or painful at significantly lower intensities compared to normal volunteers (Figure 3). This phenomenon has been described throughout the GI system, indicating a diffuse rather than a local hypersensitivity. Moreover, somatic hyposensitivity has been described in irritable bowel syndrome (IBS) patients, indicating that visceral hypersensitivity may not simply be due to some kind of reporting bias.\textsuperscript{6} In summary, visceral hypersensitivity is believed to be an important pathophysiologial mechanism in FGID. However, this phenomenon can be the result of abnormalities at any level of the BGA, from ENS to the highest cortical brain areas. It is likely that the disturbance in the BGA underlying visceral hypersensitivity differs between FGID patients. In some patients, sensitization of peripheral afferent neurons (secondary to, for example, infection) will be the key feature, in others sensitization at the level of the spinal cord could be more important. We will focus here on the evidence regarding abnormal processing or modulation of sensory information at brain level which could account for the frequently observed visceral hypersensitivity.\textsuperscript{6--9} Modulation of visceral sensory information in the brain can occur at several levels: from ‘lower-order’, automatically generated responses to ‘higher-order’ modulation resulting from cognitive processing and integration of the visceral sensory information with information from various other sources.\textsuperscript{35} For example, hypervigilance to visceral stimuli has been reported in FGID patients.\textsuperscript{10} This abnormal processing or modulation may result in abnormal autonomic and behavioral responses, which further contribute to FGID symptoms.\textsuperscript{9,19}
Differences in brain responses to visceral sensory information between FGID patients and controls: evidence from neuroimaging studies

Until today, there have been several brain imaging studies comparing the CNS activation patterns during visceral stimulation in patients with FGID versus healthy controls. The results of these studies are varying, due to the heterogeneity of the patient population and the methodology used. However, the data reported do confirm the involvement of the brain regions discussed above, although the exact nature of the differences in CNS processing of visceral afferent information between patients with FGID and controls remains incompletely understood and needs further study. In future research, it will be important to study more homogenous subgroups of patients, based on pathophysiological rather than the current symptomatic criteria. We’ll provide an overview of the studies performed so far.

The first study regarding this topic was performed by Silverman et al using PET. During both actual and simulated painful rectal stimulation, IBS patients failed to activate the perigenual ACC (BA 24, 32) compared to the control population but higher activation in the left PFC (mainly BA 10) was seen. The decreased ACC activation has been replicated in other studies afterwards and can be interpreted as evidence for dysfunction of descending pain inhibitory mechanisms, whereas the increased PFC activity could be the result of increased attention or cognitive processing.

In contrast, Mertz et al in a study using fMRI, found greater perigenual ACC (BA 24, 32) activation during painful compared to non-painful stimulation in IBS patients, but not in controls. This greater activation correlates with increased subjective pain reports. Interestingly, higher activation in the thalamus was also observed, possibly suggesting a more intense afferent signal from the gut to the thalamus in IBS patients. No significant differences in IC or PFC response were found.

Naliboff et al studied brain responses to both anticipated and actually delivered rectal balloon distension of nonnoxious intensity in IBS patients compared to controls.
using PET.\textsuperscript{40} In general, responses to actual distension and anticipation were similar within but not between the two groups.\textsuperscript{40} First, IBS patients showed preferential activation of the right LPFC and OPFC (BA 10, 11), whereas the control subjects showed bilateral activation of these structures. Right-sided activation has been associated with negative emotional processing and higher autonomic responses.\textsuperscript{40} Second, IBS patients activated the PCC significantly more than controls. Although this region has been mainly linked to cognitive processing, evidence for a role in emotional functioning or the interaction between emotion and cognition (for example, activation during cognitive processing of unpleasant stimuli) is growing.\textsuperscript{31,40} Finally, IBS patients showed decreased activation of both perigenual ACC (BA 24) and PAG, whereas activation in the caudal ACC (BA 24) was higher.\textsuperscript{40}

Bonaz et al found a strong variability of CNS responses to rectal pain between IBS patients, which provides further evidence for the hypothesis that IBS is a pathophysiologically heterogeneous disease concept. Furthermore, significant deactivations were found within the IC, the amygdala and the striatum, all in the right hemisphere, in IBS patients compared to controls.\textsuperscript{41}

Bernstein et al compared CNS responses to physiological and painful stimuli between normal controls, IBS patients and patients with inflammatory bowel disease (IBD). In summary, ACC activation was significantly higher in the control group compared to the IBS group and in the IBS group compared to the IBD group. Moreover, significant deactivation of left S1 was found in IBS patients compared to the two other groups. Controls showed more deactivation of OPFC and MPFC compared to the disease groups, although the difference was only borderline significant.\textsuperscript{42}

In a recent PET study, Naliboff et al showed significant differences in CNS processing of anticipated and delivered visceral stimulation between male and female IBS patients. Briefly, male patients showed greater activation of CNS regions known to be involved in cognitive processes (DLPFC) and in the control of autonomic and/or antinociceptive responses (LC, PAG, IC). Female patients, on the contrary, showed greater activation in regions important for affective processing and autonomic regulation (peri- and infragenual ACC, MPFC, amygdala).\textsuperscript{27}

Chang et al compared brain responses to visceral and somatic stimuli in IBS patients with and without fibromyalgia (FM). Patients with IBS alone showed a greater activation in the middle ACC in response to noxious visceral sensation, whereas the patients with comorbid FM showed a similar activation in response to somatic stimuli.\textsuperscript{29}

In summary, functional brain imaging studies in FGID have shown abnormal CNS activation patterns in response to visceral stimuli, mainly in the affective-motivational pain systems of the brain. The exact implications of these findings for FGID pathophysiology remain unclear, as these abnormalities can be caused by abnormal afferent input as well as dysfunction of the brain regions themselves (increased attention to visceral stimuli, abnormal cognitive or affective processing of normal afferent input, comorbid psychiatric disorders causing dysfunction, etc.). The role of psychosocial factors, stress and comorbid psychiatric disorders in the pathophysiology of FGID will be discussed in the next chapter.

THE ROLE OF PSYCHOSOCIAL FACTORS, PSYCHIATRIC DISORDERS AND STRESS IN FGID: EVIDENCE FOR COMMON PATHOPHYSIOLOGY?

Historically, bodily (especially autonomic, visceral) responses to arousing stimuli and feedback from the viscera to the brain (interoception) have been considered as being
crucial elements of emotions for more than 100 years. \(^43–45\) Moreover, it is well known that visceral responses can be conditioned in a classical, Pavlovian way and that interoceptive processes play a major role in this process. This kind of ‘interoceptive conditioning’ is a largely unconscious process. \(^43,44\) Recent research on emotions provides evidence for the existence of distinct neural circuits involved in different emotions, each generating emotion-specific patterns of autonomic and endocrine output to the body in general and the viscera more specifically. \(^10,44\) For example, the work of LeDoux and others shows that the amygdala is critically involved in the circuit underlying fear. \(^44\) This all points towards an important interaction between emotions and visceral sensorimotor function at brain level.

In the previous section, we described what is currently known about the differences in neural correlates of visceral sensation (including pain) between healthy subjects and FGID patients. Almost all of the regions critically involved are also reported to show abnormal activation patterns in psychiatric disorders, especially mood and anxiety disorders. \(^12–14,28,33,34\) Moreover, there is a high comorbidity of these psychiatric disorders in FGID. \(^1,3,12–14,20\) That doesn’t necessarily mean, however, that the pathophysiology underlying mood and anxiety disorders and FGID is the same.

**Practice points**

- Visceral hypersensitivity is an important feature of patients with functional bowel disorders. Both central and peripheral factors could be involved.
- Functional brain imaging studies in patients with functional bowel disorders have shown abnormal CNS activation patterns in response to visceral stimuli, mainly in the affective-motivational pain systems of the brain.
- The high prevalence of comorbid psychiatric disorders suggests that shared pathophysiological mechanisms for FGID and mood or anxiety disorders could be involved.

**Psychosocial factors and comorbid psychiatric disorders in FGID**

It is generally accepted that psychosocial stressors, whether acute or more sustained, frequently precede the onset and/or exacerbations of FGID symptoms, but they also influence health-care seeking behavior and treatment outcome. \(^1,12,31\) Moreover, severe early life stress, especially physical or sexual abuse, is common in FGID patients, with reported rates up to 40%. These findings are not specific to FGID patients, \(^1,3,12,31\) but are also reported in patients with psychiatric disorders or other functional somatic syndromes like fibromyalgia or chronic fatigue syndrome. \(^48\) The same remark can be made for the often reported association between certain personality factors like neuroticism or coping style and FGID. \(^1\)

50–90% of IBS patients in gastroenterology clinics have at least one psychiatric disorder, especially mood disorders, anxiety disorders and somatoform disorders. \(^1,12,13,20,48\) The question whether this high comorbidity is due to the well-known influence of psychiatric disorders on health-care seeking behavior, remains to be answered. \(^1,12,13\) There is growing evidence from population-based studies that the prevalence of psychiatric disorders is higher in subjects with FGID, even if in those who do not seek treatment, compared to controls, although this has not been confirmed in all studies. \(^12,13,46,48\) Moreover, severity and duration of abdominal pain may be a stronger predictor of health-care seeking behavior than psychological factors.
or psychiatric comorbidity. Furthermore, psychiatric patients suffering from mood or anxiety disorders have a higher prevalence of FGID symptoms compared to controls. There seems to be a reciprocal interaction between FGID and affective symptoms: comorbid anxiety and depression may worsen FGID symptom reports and vice versa and psychiatric comorbidity determines FGID treatment outcome. Finally, both psychotherapy and antidepressants are effective treatments of both FGID and mood/anxiety disorders, although it is not clear whether antidepressants exert their effect through central or peripheral mechanisms or whether they improve FGID symptoms independent of their antidepressant or anxiolytic effect. In summary, most of these findings may be consistent with shared pathophysiological mechanisms for FGID and mood or anxiety disorders. It is unlikely that psychiatric disorders are only epiphenomena to FGID or only important in determining health-care seeking behavior.

The neurobiology of stress and arousal systems: a potential pathophysiological link?

Stress has been traditionally seen as a pure ‘psychological’ phenomenon, associated with feelings like fear or anger. Nowadays, stress is broadly defined as ‘any threat to the homeostasis of an organism, be it real (physical) or perceived (psychological), which may be posed by events in the outside world or from within’. In the last two decades the biological underpinnings of the stress system in health and disease have become more and more clear. The hypothalamic–pituitary–adrenal (HPA) axis is critically involved. Corticotropin-releasing hormone (CRH) is synthesised by the PVN of the hypothalamus (mainly in response to ‘physiological’ stress) and transported to the pituitary, where it stimulates the release of adrenocorticotropin (ACTH) into the bloodstream. The target organ of ACTH is the adrenal cortex, where the secretion of cortisol is stimulated. Cortisol has a lot of systemic effects which are helpful in acute stress situations. Moreover, it acts as a negative feedback regulator at different levels of the HPA-axis (hypothalamus, pituitary but also hippocampus). Importantly, CRH is not only synthesised in the hypothalamus, but also in various other brain regions. In the central nucleus of the amygdala, it is synthesised mainly in response to ‘psychological’ stress, where it plays an important role in emotional (fear), behavioral and autonomic responses to stress. There are reciprocal CRH-mediated interactions between the PVN and the amygdala on one hand and the LC on the other hand, providing evidence for a bidirectional positive feedback loop between CRH (stress) and ascending noradrenergic (NA) arousal systems. As the LC is connected to visceral sensory and motor nuclei, this may provide

Research agenda

- it remains to be investigated whether psychological influences on symptom reporting or a true neurobiological disorder explain the comorbidity of both mood or anxiety disorders and FGID
- it remains to be investigated whether alterations in the highly interacting arousal and stress response systems, caused by early trauma or chronic stress in adult life, provide a potential common pathophysiological basis for both mood or anxiety disorders and FGID
a biological pathway explaining the influence of anxiety, arousal and stress on visceral sensorimotor functions. \(^{10,12,13,20}\)

It is now generally accepted that both early trauma and chronic severe stress in adult life can cause long-lasting, potentially irreversible changes in the stress response system. \(^{50}\) For example, due to chronic stress, the negative feedback system, mediated by cortisol, may fail and positive feedback mediated by arousal systems and the amygdala may become more important, resulting in HPA-axis overactivity. \(^{50}\) Furthermore, women with a history of sexual or physical abuse exhibit increased HPA-axis and autonomic responses to stress. \(^{50}\) There is growing evidence for HPA-axis abnormalities in psychiatric disorders. For example, major depressive disorder is associated with CRH hyperdrive and a diminished feedback system, resulting in high concentrations of cortisol. PTSD is also associated with CRH hyperdrive but, in contrary to MDD, this is accompanied by enhanced negative feedback, resulting in lower concentrations of cortisol. As brain regions involved in the regulation of mood (and visceral sensation) (hippocampus, MPFC) express cortisol receptors, abnormal levels of cortisol can cause changes in these structures, resulting in mood disorders, abnormal visceral sensation, or both. \(^{10,51}\) In functional somatic syndromes like chronic fatigue syndrome (CFS) a hypofunction of the whole stress response system including CRH is found. \(^{50}\)

Evidence for an influence of the stress hormone system on the physiology of the gastrointestinal tract is growing, mainly from animal research but also from preliminary human studies. For example, neonatal maternal separation in rats predisposes them to develop colonic barrier dysfunction, visceral hyperalgesia (both probably CRH-mediated), reduced somatic algesia and increased colonic motility in response to psychosocial stress. \(^{52–54}\) Furthermore, it is well-known that stress hormones play a major role in modulation of immune responses. Thus, subjects under chronic stress are more vulnerable to intestinal infection and inflammation, which can be an important pathophysiological mechanism in postinfectious FGID. \(^{55}\) Recently, it has been shown that stress-induced inhibition of gastric emptying and stimulation of colonic motor function is mediated by stimulation of brain CRH-receptors, as well as the anxiogenic responses to stress. \(^{56}\) Thus, CRH-receptor antagonists are promising drugs in the treatment of both FGID and mood or anxiety disorders. \(^{50,51,56}\) Finally, there is preliminary evidence from clinical studies in humans for alterations in HPA-axis in IBS patients, although the exact results have been conflicting. \(^{10}\)

In summary, alterations in the highly interacting arousal and stress response systems, caused by early trauma or chronic stress in adult life, provide a potential common pathophysiological mechanism of both mood or anxiety disorders and FGID. Pathological stress responses can exert their influence at any level of the BGA, for example by inducing alterations in brain regions critically involved in regulation of mood or anxiety as well as visceral sensation (hippocampus, amygdala, MPFC) or by influencing ANS output to the viscera (via the hypothalamus and/or LC).

Towards an integrative, biopsychosocial model of FGID

There is a large body of evidence that all the possible pathophysiological mechanisms in FGID (visceral hypersensitivity, stress and arousal mechanisms, ANS dysfunction, psychological traits, hypervigilance to visceral stimuli, etc.) highly interact. \(^{48}\) This provides support for a biopsychosocial model of FGID (which is also widely accepted in psychiatric disorders). In this model, FGID are seen as having a multifactorial, bidirectional rather than a unicausal, unidirectional etiology. The reciprocal interaction
between ‘biological’ factors (gut motility and/or sensitivity, genetics) and ‘psychosocial’ factors (severe life stress, personality traits, coping skills, social support) accounts for the symptoms experienced by FGID patients and their behavioral responses to these experiences and, ultimately, the treatment outcome. Moreover, the difference between ‘biological’ and ‘psychosocial’ factors is getting vague and may not be very useful, as biological mechanisms underlying “psychological” phenomena are becoming clear (neurobiological circuits underlying emotions, the stress system physiology, etc.). The BGA serves as the anatomical substrate mediating this reciprocal interactions. It seems quite clear that some factors play a more important role than others in certain subgroups of FGID patients, accounting for the heterogeneity of the population. A ‘dual-etioloogy’ hypothesis is proposed by Whitehead et al creating two subgroups of FGID patients (one with a predominantly biological etiology, another with a predominantly psychological etiology). Although probably useful for research or clinical purposes, this hypothesis may carry the danger of Cartesian dualism so deeply rooted in medicine, whereas the findings mentioned above provide evidence for finally abandoning this dualist view on functional somatic syndromes.

In line with a biopsychosocial model of FGID (and psychiatric disorders), it is useful to distinguish between risk factors (genetics, early life stress, personality development), trigger factors (psychosocial stress in adult life, infection) and perpetuating factors (coping style, anxiety or interoceptive conditioning). In this stress-vulnerability model, all factors can be either biological, psychological or social in nature.

The description of the BGA axis in this article, with particular emphasis on the CNS part, makes clear that there is a high degree of mutual interaction between visceral afferent input signals, arousal and stress systems, circuits involved in emotional and cognitive functioning and finally centers regulating autonomic output back to the viscera and behavioral responses. This provides a rough neurobiological framework for the reciprocal interaction between biological, psychological and social interactions in FGID.

Mayer et al try to summarize the evidence, proposing a ‘conceptual model of IBS based on the enhanced responsiveness of limbic circuits in the brain to stressors and emotional stimuli’, although this model remains relatively speculative. The ‘Emotional Motor System’ (EMS) is the central concept in this model, consisting of the PVN of the hypothalamus, the amygdala, the PAG and their main in- and output circuits. The EMS receives direct input from visceral and somatic afferent nerves and from cortical structures like the peri- and infragenual ACC, the IC and the OPFC and MPFC. Thus, the EMS structures receive information about the viscera (‘interoceptive (physiological) stress’, like infection, inflammation, abnormal motility) directly (making fast, autonomic responses possible), but also from higher-order structures (ACC, PFC, IC) which add emotional and cognitive elements to the visceral sensory input, making the choice of the most appropriate autonomous and behavioral response possible. Furthermore, ‘exteroceptive (psychological) stress’, like life events, reaches the EMS via the various sensory systems. Both kinds of stressors can cause long-lasting alterations in the EMS structures and their effector pathways. The EMS has three main effector pathways. First, the output to the pituitary regulates neuroendocrine responses to stressors, influencing gut and CNS physiology. Second, the PAG modulates incoming sensory information from, among others, the gut. Third, the output to the pontomedullary nuclei regulates the autonomic responses to various kinds of stressors, highly important for gut motility and secretion. Like already mentioned before, the EMS has a reciprocal, CRH-mediated positive feedback interaction with the LC NA system, regulating vigilance and arousal. Hypervigilance to visceral stimuli and hyperarousal in general are frequently seen in FGID and psychiatric patients.
Projections to higher cortical regions (for example PFC) may account for the conscious 'emotional feelings'. Pathological alterations in this EMS system and/or his in- and output structures, caused by various kinds of stressors, may provide a common pathophysiological substrate for both FGID and psychiatric disorders.

SUMMARY

It is generally accepted that FGID result from disturbance at some level of the brain–gut axis. Visceral pain is the most commonly reported symptom. The brain–gut axis roughly consists of three parts: the enteric nervous system, the autonomous nervous system and the central nervous system (spinal cord, brain). The autonomous nervous system transfers information from the gut to the brain via vagal and spinal afferent pathways. At brain level, the information is processed (affective and cognitive dimensions are added to it). Finally, the brain sends information back to the gut via the autonomous nervous system (parasympathetic and sympathetic efferents). The brain regions most consistently reported to be involved in the processing of visceral sensation and/or pain are the secondary somatosensory cortex, the insular cortex, the orbital and medial prefrontal cortices and the anterior cingulate cortex. The IC, OPFC, MPFC and the infra- and perigenual ACC subdivisions are also important in mood regulation, which indicates that emotional and visceral sensory information is integrated at this level. FGID patients show different responses to visceral stimuli in these brain regions, compared to controls.

Psychosocial stress highly influences the onset and course of FGID. Moreover, mood and anxiety disorders are frequently associated with FGID. As already described above, psychiatric disorders and FGID may share neurobiological correlates. There is growing evidence that both 'psychological' and 'physiological' stress can cause alterations in central nervous systems structures involved in mood and anxiety disorders as well as FGID, providing neurobiological evidence for a biopsychosocial theory of FGID.

REFERENCES


