Online Submissions: wjg.wjgnet.com
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2007 July 7; 13(25): 3438-3445
World Journal of Gastroenterology ISSN 1007-9327

TOPIC HIGHLIGHT

Paul Enck, Dr, Professor, *Series Editor*

Functional brain imaging of gastrointestinal sensation in health and disease

Lukas Van Oudenhove, Steven J Coen, Qasim Aziz

Lukas Van Oudenhove, Department of Neurosciences, Division of Psychiatry & Department of Pathophysiology, Gastroenterology Section, University Hospital Gasthuisberg, University of Leuven, Belgium
Lukas Van Oudenhove, Qasim Aziz, Division of Neuroscience & Medicine, Department of GI Sciences, Hope Hospital, University of Manchester, United Kingdom
Steven J Coen, Centre for Neuroimaging Sciences, Institute of Psychiatry, London, United Kingdom
Correspondence to: Dr. Lukas Van Oudenhove, Secretary of Liaison Psychiatry, University Hospital Gasthuisberg; Herestraat 49, B-3000 Leuven,
Belgium. lukas.vanoudenhove@med.kuleuven.be
Telephone: +32-16-348745 Fax: + 32-16-348700
Received: 2007-03-09 Accepted: 2007-03-12

Abstract

It has since long been known, from everyday experience as well as from animal and human studies, that psychological processes-both affective and cognitive-exert an influence on gastrointestinal sensorimotor function. More specifically, a link between psychological factors and visceral hypersensitivity has been suggested, mainly based on research in functional gastrointestinal disorder patients. However, until recently, the exact nature of this putative relationship remained unclear, mainly due to a lack of non-invasive methods to study the (neurobiological) mechanisms underlying this relationship in non-sleeping humans. As functional brain imaging, introduced in visceral sensory neuroscience some 10 years ago, does provide a method for *in vivo* study of brain-gut interactions, insight into the neurobiological mechanisms underlying visceral sensation in general and the influence of psychological factors more particularly, has rapidly grown. In this article, an overview of brain imaging evidence on gastrointestinal sensation will be given, with special emphasis on the brain mechanisms underlying the interaction between affective & cognitive processes and visceral sensation. First, the reciprocal neural pathways between the brain and the gut (brain-gut axis) will be briefly outlined, including brain imaging evidence in healthy volunteers. Second, functional brain imaging studies assessing the influence of psychological factors on brain processing of visceral sensation in healthy humans will be discussed in more detail. Finally, brain imaging work investigating differences in brain responses to visceral distension between healthy volunteers and functional gastrointestinal disorder patients will be highlighted.

Key words: Functional brain imaging; Functional gastro-intestinal disorders; Visceral hypersensitivity; Gastrointestinal sensation; Psychological factors

Van Oudenhove L, Coen SJ, Aziz Q. Functional brain imaging of gastrointestinal sensation in health and disease. *World J Gastroenterol* 2007; 13(25): 3438-3445

http://www.wjgnet.com/1007-9327/13/3438.asp

INTRODUCTION

It has since long been suggested that psychological processes may influence gastrointestinal (GI) sensory and motor function, both in the medical literature and by lay persons in everyday life. Most people seem to have at least some experience with changes in GI sensorimotor function during "stress" or emotional arousal, which may lead to abdominal symptoms. This knowledge or experience is expressed in sayings in many different languages, including "butterflies in the stomach" in English. In 1833, William Beaumont observed changes in gastric mucosa during emotional stress in a patient with a gastric fistula[1]. In 1909, Sir Walter Cannon stated, based on his experiments in cats, that "gastric and intestinal peristalsis are stopped in man as they are stopped in the lower animals, by worry and anxiety and the major affective states"[2] (cited in[3]). These early observations, although obviously methodologically flawed by modern standards, provide nevertheless some indication of a putative influence of psychological factors (and thus the brain) on the gut.

This body of old preliminary evidence has, however, been strengthened by more recent and methodologically stronger human research in both healthy volunteers and patients with functional gastrointestinal disorders (FGID).

In healthy volunteers, various forms of "stress"(including, among others, experimentally induced anxiety and acoustic stress) have been found to influence esophageal[4], gastric[5,6] and rectal[7,8] sensorimotor function and/or symptoms. For example, experimentally induced anxiety is associated with significantly lower gastric compliance and accommodation during barostat testing, as

well as with higher ratings for some epigastric symptoms during a nutrient drinking test[6]. Moreover, the magnitude of visceral pain hypersensitivity after distal oesophageal acidification correlates with pre-study anxiety state scores[4].

Even more evidence is coming from studies in FGID patients. As a lot of these patients are characterized by both visceral hypersensitivity[9-11] and psychological-affective and cognitive-abnormalities[12-16], a link between both can be hypothesized. For example, in functional dyspepsia, an association between gastric hypersensitivity and neuroticism, history of abuse and somatization has been reported[17,18]. Furthermore, anxiety levels at the moment of barostat investigation are negatively correlated with gastric discomfort and pain thresholds, but only in the hypersensitive subgroup of patients, highlighting the complexity of this relationship in a heterogeneous disorder[19]. In summary, the exact nature of a putative (causal?) link between psychological processes or abnormalities and visceral hypersensitivity remains incompletely understood. Theoretically, visceral hypersensitivity could result from sensitization of peripheral nerves or dorsal horn neurons in the spinal chord as well as from abnormal cortical processing-whether or not due to psychological processes-of normal afferent signals[11]. It is conceivable that both mechanisms could be involved, with their relative importance varying in different individual patients, although clear direct evidence for this hypothesis is lacking. In the past, the lack of tools for studying brain-gut interactions *in vivo*, caused great difficulty in answering this question.

Functional brain imaging (FBI), mainly Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI), has been introduced in visceral sensory neuroscience roughly 10 years ago. As FBG does provide a method for *in vivo* study of brain-gut interactions, insight into the neurobiological mechanisms underlying visceral sensation in general and the influence of psychological factors more particularly, has rapidly grown. The aim of this article is to provide an overview of brain imaging evidence on GI sensation, with special emphasis on the brain mechanisms of the interaction between cognitive-affective processes and visceral sensation. First, the reciprocal neural pathways between the brain and the gut (brain-gut axis) will be briefly outlined, including evidence from brain imaging studies in healthy volunteers. Second, FBI studies assessing the influence of psychological factors on brain processing of visceral sensation in healthy humans will be discussed in more detail. Finally, brain imaging work investigating differences in brain response to GI distension between healthy volunteers and FGID patients will be highlighted.

THE BRAIN-GUT AXIS

The brain-gut axis (BGA) can be defined as the bidirectional "communication system" between the gut and the brain. It is important to note that not only neural (autonomic nervous system, ANS), but also neuroendocrine (hypothalamo-pituitary-adrenal (HPA) axis) and neuroimmune pathways are involved. As extensive reviews on the BGA have been published before[13,20,21], we will only give a summary here, mainly limited to neural pathways.

The evidence presented is based partly on invasive and/or post mortem studies in animals, but mainly on *in vivo* brain imaging studies on somatic (reviewed in[22]) and visceral sensation and pain (reviewed in[13,23]) in humans. In brain imaging studies on visceral sensation and pain, different visceral stimulation methods have been used (mainly balloon distension of some part of the GI tract[24-26], but also electrical stimulation[27], acid infusion in the esophagus[28] and intragastric nutrient infusion[29,30] to mimic more physiological conditions). Moreover, different neuroimaging modalities (mainly PET & fMRI) and analysis methods have been used. Furthermore, different parts of the GI tract have been stimulated, including the esophagus[25,31-33], the gastric fundus[24,34] and antrum[35] and the sigmoid-rectum[26,36,37]. Finally, different intensities of stimulation have been used (non-painful versus painful). As a consequence of this heterogeneity, variability of results is relatively high, which makes it sometimes difficult to compare different studies. However, in healthy humans, the cortical "visceral sensory neuromatrix" has been outlined fairly consistently. Furthermore, a recent high-resolution fMRI study has provided support for processing of visceral sensory information in specific brainstem regions[38].

There are two important distinct systems transferring visceral sensory signals from the gut to the brain, the vagal and the spinal afferent system.

The vagal ("parasympathetic") afferent system

Vagal primary afferent neurons mainly project to the nucleus of the solitary tract (NTS), from which secondary projections ascend to the thalamus (mostly through the parabrachial nucleus) and directly to brain structures including the hypothalamus, locus coeruleus (LC)[38]-amygdala system and periaqueductal gray (PAG)[38], which are known to be involved in arousal and emotional, autonomic, neuroendocrine and behavioural responses. From the thalamus, third order neurons relay sensory signals from the gut to the cortical "visceral sensory neuromatrix", which will be described below[13,20,21,23].

The spinal ("sympathetic") afferent system

Primary spinal visceral afferent nerves make synapse in the dorsal horn of the spinal cord. Secondary neurons project proximally along the spinal cord through the spinoreticular, spinomesencephalic, spinohypothalamic and spinothalamic tracts[13,21,39]. The first three of these tracts generally activate reflexive/unconscious/automatic responses to visceral sensory input (arousal, autonomic responses, prototype emotional and behavioural responses)[13,21,39]. The spinothalamic tract is the most important pathway, projecting to the cortex, where conscious visceral sensation arises. It projects to the ventral posterior lateral, medial dorsal and ventral medial posterior nuclei of the sensory thalamus, from which tertiary neurons relay GI sensory signals to the somatosensory cortices (S Ⅰ/S Ⅱ), the cingulate cortex and the insula, respectively[13,21,39]. The

prefrontal cortex (PFC) is probably the highest integrative structure processing (visceral) sensory/pain signals, which is also crucially involved in selecting and generating responses to this sensory input[40].

The cerebral cortex: the "visceral sensory/pain neuromatrix"

The main function of SⅠ/SⅡ ("lateral pain system") is to encode intensity and localisation of (visceral) stimuli (sensory-discriminative pain dimension), whereas the cingulate cortex ("medial pain system") is mainly involved in the affective-motivational (pain unpleasantness, pain-related anxiety…) and cognitive-evaluative (attention, anticipation…) dimensions of pain[41-43]. However, the distinction between and within both systems may be less clear than thought[43]. Certainly, important interactions between both systems exist[40]. Moreover, the relative importance of SⅠ/SⅡ in visceral versus somatic pain has been a matter of debate, due to conflicting results regarding this issue[24,34,44-48].

The cingulate cortex is a multifunctional structure that can be divided into several anatomical and functional subregions, the most important in this context being[23,49,50]: (1) anterior cingulate cortex (ACC, sometimes described as "ventral ACC"), to be further subdivided in: (a) pregenual ACC (pACC); (b) subgenual ACC (sACC). (2) mid-cingulate cortex (MCC), to be further subdivided in: (a) anterior (aMCC, sometimes described as "dorsal ACC", or "midACC"); (b) posterior (pMCC) parts.

However, different ways of subdividing the cingulate cortex have been proposed and used[51,52], making comparisons between studies difficult and sometimes confusing, especially when Brodmann areas and/or stereotactic coordinates are not mentioned. In this paper, we have tried to use the cingulate subdivision proposed by Vogt *et al*[49,50] as described above consistently, because it is firmly grounded in converging evidence from cytoarchitectonic as well as functional neuroimaging studies, but we will also quote the name of the cingulate subregion as mentioned in the original article where possible. There is, however, large consensus that the cingulate cortex, through its different subregions, is playing a role in encoding the affective-motivational dimension of pain, in generating autonomic, emotional, behavioural and descending modulatory responses to (visceral) pain[13,39,43,49,50,53] as well as in anticipation of or attention to aversive (visceral) stimuli[33,43,49,50,54-56].

The insula has been termed the "interoceptive cortex", where sensory information, from different modalities, about the internal state of the organism is processed[47,57]. It is thus not a pain-specific region, although it may be involved in encoding sensory, but also affective dimensions of pain[23,43], thus integrating visceral and somatic sensory input with emotional information[13,23]. Efferent output from the insula to the amygdala, hypothalamus, PAG and other brainstem regions is involved in higher order control of autonomic visceromotor responses[13,23].

The prefrontal cortex (PFC) is a complex cortical region consisting of several subdivisions. The PFC is believed to be mainly important in cognitive influences on pain as well as (secondary) pain affect[22,40]. Generally, the orbitofrontal cortex (OFC) integrates sensory information from different modalities (including information from visceral sources[24,48]) and encodes its affective, motivational, reward and hedonic valence[58]. The OFC also controls the choice between and the generation of autonomic and behavioral response patterns[59]. It has been shown to be a putative biological substrate of the interaction between cognition on one hand (including placebo effect-expectation of relief, attention-distraction, anticipation) and emotions and (visceral) pain on the other hand[51,53,60,61]. The dorsolateral prefrontal cortex (DLPFC) is believed to be a more purely cognitive region, involved in working memory and complex attention tasks[62], including anticipation of and attention to (visceral) sensation and pain[31,43]. More specifically, the right ventrolateral prefrontal cortex (RVLPFC) has been shown to be involved in higher control of endogenous pain inhibition (through connections with the PAG), whereas the dorsomedial prefrontal cortex (DMPFC) has been implicated in anticipatory and emotional responses to pain and pain facilitation[37,51,54].

Descending modulatory pathways

Most brain structures receiving visceral sensory/pain inputs project back to modulate ongoing transmission of those inputs, mainly at the level of the dorsal horn of the spinal cord[21,63-65]. The ACC is believed to be the key cortical region involved in descending modulatory control, projecting to the amygdala and the PAG, another key pain modulatory region[38,51,63,64,66]. Thus, cognitive and affective factors may exert influence on pain transmission through the ACC[51]. The amygdala and the PAG project to the noradrenergic locus coeruleus, the serotonergic raphe nuclei and the rostrolateral ventral medulla, which in turn send projections to the dorsal horn of the spinal cord, influencing the synaptic transmission of sensory information at this level ("gate mechanism")[21,63]. Endogenous opioids are crucially involved in this system at all levels, together with other neurotransmitters including serotonin and noradrenalin[51,63]. Taken together, this descending modulatory system may be an important neurobiological substrate of the influence of psychological factors on pain.

It is interesting to note, that almost all the regions processing (visceral) sensory information described above, are also crucially involved in emotional perception-identification, generation and regulation[67-69], providing a neurobiological as well as a conceptual link between visceral sensation and emotion.

INFLUENCE OF PSYCHOLOGICAL FACTORS ON BRAIN PROCESSING OF VISCERAL SENSATION IN HEALTHY HUMANS

Phillips *et al*[32] investigated neural responses to non-painful esophageal stimulation during negative versus neutral emotional context created by viewing of standardized

fearful versus neutral facial expressions[70]. Activation in the bilateral aMCC ("dorsal ACC") and the right anterior insular cortex were found to be significantly higher in the negative emotional condition. In a second fMRI experiment reported in the same article, brain activation during non-painful esophageal distension was significantly higher in the left aMCC ("dorsal ACC") and the bilateral insula when viewing high-intensity versus low-intensity fearful facial expressions. Moreover, the high-intensity emotional condition was associated with significantly higher reports of discomfort and anxiety, compared to the low-intensity condition.

Gregory *et al*[33] studied the influence of selective attention (to the visceral or a visual stimulus) and divided attention (to both stimuli) on neural correlates of non-painful esophageal balloon distension. Selective attention to the esophageal stimulus activated SⅠ/SⅡ (sensory processing) and aMCC ("mid-ACC") (cognitive processing), whereas selective attention to the visual stimulus activated visual cortex. During divided attention, more brain regions in the (sensory and cognitive) visceral sensory network were recruited, in comparison to the visual sensory network. This study provides evidence for a substantial effect of cognitive factors as attention on visceral sensation. It also suggests that visceral sensory information may be preferentially processed in the brain compared to other sensory modalities.

Yaguez *et al*[56] looked at the brain responses during anticipation of painful esophageal stimulation using a Pavlovian classical aversive conditioning paradigm. Three differently colored circles acted as conditioned stimuli (CS) as they were paired with painful esophageal distension, air puff to the wrist and nothing (unconditioned stimuli, US). Neural activity was registered (using fMRI) during learning (pairing of CS with their respective US), anticipation (pairing CS-US in only 50% of the presentations) and extinction (CS presented without US). During the learning phase of the esophageal pain condition, the classical visceral pain matrix [SⅠ/SⅡ, aMCC ("mid-ACC"), insula] was activated. However, similar regions were activated during the anticipation and extinction phase of this condition, thus without the actual painful esophageal stimulus being delivered. Innocuous stimulation of the hand by air puff didn't show this effect. Thus, actual and anticipated visceral pain, both activate the visceral pain neuromatrix.

Taken together, these studies provide important direct evidence for extensive modulation of normal sensory signals from the gut by psychological-both affective and cognitive-processes at the level of the brain. Although this obviously does not necessarily implicate that symptoms in FGID patients can be entirely attributed to these processes, the hypothesis that they may play a role in at least some FGID patients is certainly strengthened by this work in healthy volunteers.

BRAIN IMAGING STUDIES ON VISCERAL SENSATION/PAIN IN FGID PATIENTS

Irritable Bowel Syndrome (IBS)

An extensive review of all the brain imaging studies in IBS falls beyond the scope of this article. As the older evidence, which has been reviewed earlier[13,23], is generally descriptive and methodologically less strong (no control for potential confounders as affective and cognitive factors, sex…), only a brief summary of this body of literature will be presented here. A selection of more recent and novel studies will be discussed in more detail.

It should be noted that comparing different brain imaging studies in IBS patients is even more difficult than in normal controls. Patient heterogeneity is likely to have an important influence on the results in FGID patients, especially with respect to psychosocial factors[71]. Besides, all the potential sources of variability as discussed above in the section on healthy controls also apply to FGID patients.

General brain imaging findings in IBS

However, similar brain regions were generally found to be activated during rectal distension in healthy volunteers and IBS patients (the visceral sensory/pain neuromatrix, as described above). However, the level/extent of activation differs between patients and controls, mainly in regions involved in processing the affective and cognitive dimensions of visceral sensation/pain. In some studies, ACC-aMCC activity during painful rectal distension was higher in IBS patients, compared to healthy volunteers[26,36,37,72]. These differences may be explained by upregulation of visceral afferent input to the brain, abnormal affective or cognitive responses at the brain level (increased anticipation, attention (hypervigilance) or negative affective reaction to the visceral sensory stimulus), or both. However, in a roughly equal number of studies, lower or absent ACC-aMCC activity was found during rectal distension in IBS patients compared to healthy volunteers[71,73-76]. This can again be interpreted in several ways, including decreased descending antinociceptive response through pathways originating at the level of the ACC, ceiling effects or differential sensitization of the lateral versus the medial pain system in IBS.

Somatic pain sensitivity in IBS

(Brain) responses to somatic painful stimuli have also been studied in IBS patients, again leading to somewhat contradictory results. Normal[77,78], lower[79], as well as higher[77] somatic pain thresholds, compared to controls, have been reported. Although visceral pain stimuli are generally rated as more unpleasant compared to somatic pain stimuli, Verne *et al*[72] found equally increased responses in both sensory and affective regions of the pain matrix for visceral and somatic pain stimuli in IBS patients compared to control. These findings were interpreted as supportive of increased afferent sensory signalling to the brain in IBS. Chang *et al*[80], however, found an enhanced aMCC ("middle ACC") response to visceral stimuli only in IBS patients, whereas a higher activation in the same region was found in response to somatic stimuli only in fibromyalgia (FM) patients. This may be suggestive of stimulus-specific cognitive enhancement of sensory input, rather than upregulated afferent signalling to the brain alone.

Discussion of selected brain imaging studies in IBS

Naliboff *et al*[36] found similar brain responses to actual and anticipated non-painful rectal distension in IBS patients and controls using H_2O^{15}-PET, providing important direct evidence for a role of anticipation in the perception of visceral sensation. Furthermore, a decreased response in the sACC ("infragenual ACC"), pACC ("perigenual ACC"), medial and orbital PFC and the PAG was found in IBS patients (possibly to be interpreted as a difference in affective response, failure to activate descending antinociceptive responses or inappropriate regulation of visceromotor response), whereas the aMCC ("rostral ACC") (involved in pain unpleasantness as well as cognitive influences on pain) was found to be more activated in IBS.

In a PET study, Ringel *et al*[71] reported lower ACC-aMCC ("ACC") activity during rectal distension in IBS patients with a history of abuse, compared to patients without any abuse history. However, in a more recent fMRI study[81] by the same group, in a larger patient sample, abused patients showed higher MCC ("MCC") and posterior cingulate activation compared to non-abused patients. ACC ("perigenual ACC") activation, on the contrary, was lower in abused patients compared to non-abused patients and controls. Furthermore, pain rating during distension correlated with MCC activation, thus paralleling the differences in MCC activation between abused and non-abused patients. Despite the inconsistencies, the results provide direct evidence for an important influence of psychosocial factors on brain mechanisms of visceral sensation.

Kwan *et al*[82] found that the perceptual responses to rectal stimuli are time locked to the stimulus period in healthy subjects but are dissociated from the duration and intensity of the stimulus in IBS patients. In a subsequent fMRI study[75], the same authors addressed this issue further, reporting that "percept-related activations were more extensive than stimulus-related activations in control subjects", which they explained by "better temporal "fit" with the percept compared with the stimulus pressure curve". Furthermore, low-pressure rectal distension eliciting a sensation of urge, activated S1 in IBS patients but not in controls, which could be interpreted as upregulated afferent input underlying visceral hypersensitivity (or "visceral allodynia", as stated by the authors). During high-pressure painful distension, the medial thalamus and the hippocampus were activated in IBS patients, but not in controls. The authors explain these somewhat unexpected findings as altered affective-motivational processing of pain, although the hippocampus has rarely been mentioned in this context. Finally, lack of activation in right anterior insula was found in IBS patients compared to controls during painful distension, interpreted by the authors as either a ceiling effect or a dysfunction in interoceptive processing or control of visceromotor responses.

Recently, Lawal *et al*[83] performed an fMRI study in which they investigated regional brain activation during subliminal rectal distension, i.e. below the threshold for conscious perception. The total volume of cerebral cortex activated was significantly higher in IBS patients compared to controls. The authors claimed that using subliminal stimuli allowed them to study brain processing of visceral afferent signals independent from cognitive modulation, thus providing support for the hypothesis that visceral hypersensitivity in IBS is due to increased afferent signalling to the brain rather than altered processing at the level of the brain. However, this assumption has been questioned and it has even been suggested that the study design maximized rather than minimized cognitive modulation[54]. We believe that it is indeed likely that cognitive and emotional modulation of visceral afferent signals, and thus conscious visceral sensation, may always occur in awake humans[54].

In a recent H_2O^{15}-PET-study, Mayer and co-workers[37] found no differences in insula and aMCC ("dorsal ACC, dACC" or "caudal ACC") activity between IBS patients, ulcerative colitis (UC) patients and controls during actual and anticipated rectal distension, possibly suggesting that the brain may receive similar visceral input in the three groups. Interestingly, during anticipated and delivered rectal distension, UC patients and controls generated more activation in regions known to be involved in antinociception (right VLPFC and dorsal pons/PAG) compared to IBS patients. Activation in an affective network known to be able to inhibit the PAG (and thus to exert a pronociceptive influence) [left DMPFC, left sACC ("infragenual ACC") & bilateral pACC ("rostral ACC" or "ventral ACC"), left amygdala], on the contrary, was lower in UC patients and controls compared to the IBS group. Although somewhat contrary to a previous study[36], this result may be suggestive of a failing antinociceptive response at the brain level in IBS, driven by affective factors. Finally, the antinociceptive brain response triggered by rectal distension in UC patients and controls was investigated more into detail in this study. The authors found a positive correlation between right VLPFC activation and dorsal pons/PAG activation, which was mediated by negative correlations between right VLPFC and DMPFC/ACC, which in turn was negatively correlated with dorsal pons/PAG activation.

The same group from UCLA recently published the first longitudinal H_2O^{15}-PET-study in IBS (Naliboff *et al*[84]), in which the change in brain response to repeated anticipated and delivered rectal distension was studied over a period of 12 mo. Despite stable IBS-symptom severity and mood, visceral hypersensitivity to rectal distension gradually normalized during repeated stimulus exposure. When brain activation was compared between the first and the second scanning session, anterior insula and bilateral thalamus were consistently activated during rectal distension, which is indicative of similar visceral input to the brain during both sessions. Hypothalamus and subgenual ACC ("infragenual ACC, iACC") were also consistently activated, explained by the authors as the neural substrate of stable visceromotor and autonomic responses over time. However, pregenual ACC ("supragenual ACC") and MCC activity significantly decreased during distension in the second session, interpreted by the authors as reduced vigilance and/or arousal triggered by the visceral stimulus. Connectivity analysis confirmed the covariation of a pontine/midbrain region (possibly the locus coeruleus) with the amygdala and the pACC-MCC regions, which

are part of the hypothesized arousal network in which activity decreased during the second session. However, different use of ACC subdivisions (in the text as well as in the region of interest definitions used in the PET analyses) makes the comparison between ACC activation results from this and the previously mentioned study by the same group[37] somewhat difficult. For example, the absence of group differences in "dACC" activation was interpreted as equal visceral afferent input in the three groups in the first study[37]. However, in the second study, decrease in activation in areas equivalent to the "dACC" ("supragenual ACC" and "MCC") over time are explained as reduction in arousal and vigilance[84]. Furthermore, in the first study, the "rostral" or "ventral" ACC is seen as part of an affective network involved in pain modulation, but it is not clear which is the equivalent ACC subregion in the second study[84], as the subregions are differently defined. Nevertheless, these studies provide the most interesting new insights on the relationship between visceral hypersensitivity and psychological factors including arousal, attentional phenomena and visceral-specific anxiety, providing strong evidence for an important role for these processes in the pathophysiology of IBS.

Using H_2O^{15}-PET, Lackner *et al* recently showed that cognitive behavioural therapy (CBT) is associated with a reduction of baseline activity in the right sACC and the left medial temporal lobe (including the amygdala) of IBS patients, which was accompanied by improvements in GI symptoms, anxiety and worry. These brain activity changes are explained as the biological substrate of reduced attention to visceral stimuli or visceral-specific anxiety as a result of CBT in these patients[85].

Finally, another interesting recent fMRI study showed that the tricyclic antidepressant amitryptiline, which is believed to be of clinical benefit to at least some IBS patients[86], reduces pain related cerebral activations in the pACC and the left posterior parietal cortex compared to placebo, but only during mental stress[87].

Functional dyspepsia (FD)

In FD, brain imaging evidence is far more sparse compared to IBS. To our knowledge, only one brain imaging study in FD has been performed, using H_2O^{15}-PET[88,89]. During painful gastric distension, FD patients who are hypersensitive to gastric distension showed similar activation of bilateral sensorimotor cortex (SⅠ/SⅡ) compared to controls. However, intragastric pressures and volumes were considerably lower in patients, whereas pain or discomfort scores were similar, as the stimuli were delivered at previously determined individual discomfort thresholds. This may be interpreted as a biological mechanism underlying visceral hypersensitivity in these patients, although this doesn't necessarily imply that only heightened afferent input, and not central cognitive or affective processes are involved[54,89]. Furthermore, contrary to controls, no activation of any cingulate subregion was found in FD patients, which may again be explained in several ways including failing descending antinociception and ceiling effects, as described above[89]. Interestingly, no activation was found during anticipation of an undelivered stimulus, contrary to previous findings in IBS[36,37,84]. Overall, although only subjects that had previously been shown to be hypersensitive to gastric distension were included in this study, variability in brain responses was still high, potentially due to the variability of the patient samples at the psychological level.

CONCLUSION

Functional brain imaging has provided a valuable method for studying the neural mechanisms underlying visceral sensation in awake living humans. Despite some inconsistencies and methodological difficulties, this resulted in a substantial increase in the knowledge of these mechanisms, including the role of psychological factors and their brain substrates. However, despite growing evidence for a neurobiological link between psychological abnormalities and visceral hypersensitivity in FGID patients, the answer to the question whether abnormal brain processing of visceral signals in these patients is primarily due to abnormal afferent input to the brain or abnormal processing of afferent input in the brain remains a matter of debate. It is likely, however, given the ongoing improvement in methodology and study design, that functional brain imaging will continue to provide important new information and ultimately the answer to what is arguably one of the most important questions in present FGID research.

REFERENCES

1 **Beaumont W**. Experiments and Observations on the Gastric Juice and the Physiology of Digestion. Plattsburgh: F.P. Allen, 1833
2 **Cannon W**. The influence of emotional states on the functions of the alimentary canal. *Am J Med Sci* 1909; **137**: 480-487
3 **Dunbar H**. Emotions and Bodily Changes. New York: Columbia University Press, 1938
4 **Sharma A**, Aziz Q, Delaney C, Hobson A. The magnitude of visceral pain hypersensitivity after distal oesophageal acidification correlates with pre-study anxiety state scores. *Gastroenterology* 2006; **130**: A880
5 **Camilleri M**, Malagelada JR, Kao PC, Zinsmeister AR. Gastric and autonomic responses to stress in functional dyspepsia. *Dig Dis Sci* 1986; **31**: 1169-1177
6 **Geeraerts B**, Vandenberghe J, Van Oudenhove L, Gregory LJ, Aziz Q, Dupont P, Demyttenaere K, Janssens J, Tack J. Influence of experimentally induced anxiety on gastric sensorimotor function in humans. *Gastroenterology* 2005; **129**: 1437-1444
7 **Gonlachanvit S**, Rhee J, Sun WM, Chey WD. Effect of acute acoustic stress on anorectal function sensation in healthy human. *Neurogastroenterol Motil* 2005; **17**: 222-228
8 **Posserud I**, Agerforz P, Ekman R, Björnsson ES, Abrahamsson H, Simrén M. Altered visceral perceptual and neuroendocrine response in patients with irritable bowel syndrome during mental stress. *Gut* 2004; **53**: 1102-1108
9 **Drossman DA**, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. *Gastroenterology* 2002; **123**: 2108-2131
10 **Tack J**, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004; **127**: 1239-1255
11 **Anand P**, Aziz Q, Willert R, van Oudenhove L. Peripheral and central mechanisms of visceral sensitization in man. *Neurogastroenterol Motil* 2007; **19**: 29-46
12 **Budavari AI**, Olden KW. Psychosocial aspects of functional gastrointestinal disorders. *Gastroenterol Clin North Am* 2003; **32**:

477-506
13 **Van Oudenhove L**, Demyttenaere K, Tack J, Aziz Q. Central nervous system involvement in functional gastrointestinal disorders. *Best Pract Res Clin Gastroenterol* 2004; **18**: 663-680
14 **Henningsen P**, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a meta-analytic review. *Psychosom Med* 2003; **65**: 528-533
15 **Naliboff BD**, Munakata J, Fullerton S, Gracely RH, Kodner A, Harraf F, Mayer EA. Evidence for two distinct perceptual alterations in irritable bowel syndrome. *Gut* 1997; **41**: 505-512
16 **Labus JS**, Bolus R, Chang L, Wiklund I, Naesdal J, Mayer EA, Naliboff BD. The Visceral Sensitivity Index: development and validation of a gastrointestinal symptom-specific anxiety scale. *Aliment Pharmacol Ther* 2004; **20**: 89-97
17 **Fischler B**, Tack J, De Gucht V, Shkedy ZI, Persoons P, Broekaert D, Molenberghs G, Janssens J. Heterogeneity of symptom pattern, psychosocial factors, and pathophysiological mechanisms in severe functional dyspepsia. *Gastroenterology* 2003; **124**: 903-910
18 **Geeraerts B**, Van Oudenhove L, Fischler B,. The association between gastric sensorimotor function and abuse history in functional dyspepsia. *Gastroenterology* 2005; **128** Suppl 2: A339
19 **Van Oudenhove L**, Vandenberghe J, Geeraerts B, Vos R, Persoons P, Demyttenaere K, Fischler B, Tack J. Relationship between anxiety and gastric sensorimotor function in functional dyspepsia. *Psychosom Med* 2007;**69**:455-463
20 **Aziz Q**, Thompson DG. Brain-gut axis in health and disease. *Gastroenterology* 1998; **114**: 559-578
21 **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
22 **Apkarian AV**, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* 2005; **9**: 463-484
23 **Derbyshire SW**. A systematic review of neuroimaging data during visceral stimulation. *Am J Gastroenterol* 2003; **98**: 12-20
24 **Vandenbergh J**, Dupont P, Fischler B, Bormans G, Persoons P, Janssens J, Tack J. Regional brain activation during proximal stomach distention in humans: A positron emission tomography study. *Gastroenterology* 2005; **128**: 564-573
25 **Aziz Q**, Andersson JL, Valind S, Sundin A, Hamdy S, Jones AK, Foster ER, Långström B, Thompson DG. Identification of human brain loci processing esophageal sensation using positron emission tomography. *Gastroenterology* 1997; **113**: 50-59
26 **Mertz H**, Morgan V, Tanner G, Pickens D, Price R, Shyr Y, Kessler R. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology* 2000; **118**: 842-848
27 **Frøbert O**, Arendt-Nielsen L, Bak P, Funch-Jensen P, Bagger JP. Oesophageal sensation assessed by electrical stimuli and brain evoked potentials--a new model for visceral nociception. *Gut* 1995; **37**: 603-609
28 **Kern MK**, Birn RM, Jaradeh S, Jesmanowicz A, Cox RW, Hyde JS, Shaker R. Identification and characterization of cerebral cortical response to esophageal mucosal acid exposure and distention. *Gastroenterology* 1998; **115**: 1353-1362
29 **Geeraerts B**, van Oudenhove L, Dupont P. Regional brain activation during gastric nutrient infusion in healthy volunteers. *Gastroenterology* 2006; **130**: A138-A138
30 **Kuo B**, Aaron I, Qui W. Dynamic imaging of the brain activity during feeding and epigastric discomfort/pain with a physiological gastric stimulus. *Gastroenterology* 2005; **128**: A372-A372
31 **Aziz Q**, Thompson DG, Ng VW, Hamdy S, Sarkar S, Brammer MJ, Bullmore ET, Hobson A, Tracey I, Gregory L, Simmons A, Williams SC. Cortical processing of human somatic and visceral sensation. *J Neurosci* 2000; **20**: 2657-2663
32 **Phillips ML**, Gregory LJ, Cullen S, Coen S, Ng V, Andrew C, Giampietro V, Bullmore E, Zelaya F, Amaro E, Thompson DG, Hobson AR, Williams SC, Brammer M, Aziz Q. The effect of negative emotional context on neural and behavioural responses to oesophageal stimulation. *Brain* 2003; **126**: 669-684
33 **Gregory LJ**, Yágüez L, Williams SC, Altmann C, Coen SJ, Ng V, Brammer MJ, Thompson DG, Aziz Q. Cognitive modulation of the cerebral processing of human oesophageal sensation using functional magnetic resonance imaging. *Gut* 2003; **52**: 1671-1677
34 **Lu CL**, Wu YT, Yeh TC, Chen LF, Chang FY, Lee SD, Ho LT, Hsieh JC. Neuronal correlates of gastric pain induced by fundus distension: a 3T-fMRI study. *Neurogastroenterol Motil* 2004; **16**: 575-587
35 **Ladabaum U**, Minoshima S, Hasler WL, Cross D, Chey WD, Owyang C. Gastric distention correlates with activation of multiple cortical and subcortical regions. *Gastroenterology* 2001; **120**: 369-376
36 **Naliboff BD**, Derbyshire SW, Munakata J, Berman S, Mandelkern M, Chang L, Mayer EA. Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation. *Psychosom Med* 2001; **63**: 365-375
37 **Mayer EA**, Berman S, Suyenobu B, Labus J, Mandelkern MA, Naliboff BD, Chang L. Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis. *Pain* 2005; **115**: 398-409
38 **Dunckley P**, Wise RG, Fairhurst M, Hobden P, Aziz Q, Chang L, Tracey I. A comparison of visceral and somatic pain processing in the human brainstem using functional magnetic resonance imaging. *J Neurosci* 2005; **25**: 7333-7341
39 **Almeida TF**, Roizenblatt S, Tufik S. Afferent pain pathways: a neuroanatomical review. *Brain Res* 2004; **1000**: 40-56
40 **Price DD**. Psychological and neural mechanisms of the affective dimension of pain. *Science* 2000; **288**: 1769-1772
41 **Kulkarni B**, Bentley DE, Elliott R, Youell P, Watson A, Derbyshire SW, Frackowiak RS, Friston KJ, Jones AK. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. *Eur J Neurosci* 2005; **21**: 3133-3142
42 **Jones AK**, Kulkarni B, Derbyshire SW. Pain mechanisms and their disorders. *Br Med Bull* 2003; **65**: 83-93
43 **Peyron R**, Laurent B, García-Larrea L. Functional imaging of brain responses to pain. A review and meta-analysis(2000). *Neurophysiol Clin* 2000; **30**: 263-288
44 **Lu CL**, Chang FY, Hsieh JC. Is somatosensory cortex activated during proximal stomach stimulation and the role of insula in visceral pain. *Gastroenterology* 2005; **128**: 1529-1530; author reply 1530-1531
45 **Van Oudenhove L**, Dupont P, Vandenberghe J, Geeraerts B, Tack J. Is Somatosensory Cortex Activated during Proximal Stomach Stimulation and the Role of Insula in Visceral Pain - Reply to Lu et al. *Gastroenterology* 2005; **128**: 1530-1531
46 **Strigo IA**, Duncan GH, Boivin M, Bushnell MC. Differentiation of visceral and cutaneous pain in the human brain. *J Neurophysiol* 2003; **89**: 3294-3303
47 **Eickhoff SB**, Lotze M, Wietek B, Amunts K, Enck P, Zilles K. Segregation of visceral and somatosensory afferents: an fMRI and cytoarchitectonic mapping study. *Neuroimage* 2006; **31**: 1004-1014
48 **Lotze M**, Wietek B, Birbaumer N, Ehrhardt J, Grodd W, Enck P. Cerebral activation during anal and rectal stimulation. *Neuroimage* 2001; **14**: 1027-1034
49 **Vogt BA**. Pain and emotion interactions in subregions of the cingulate gyrus. *Nat Rev Neurosci* 2005; **6**: 533-544
50 **Vogt BA**, Berger GR, Derbyshire SW. Structural and functional dichotomy of human midcingulate cortex. *Eur J Neurosci* 2003; **18**: 3134-3144
51 **Petrovic P**, Ingvar M. Imaging cognitive modulation of pain processing. *Pain* 2002; **95**: 1-5
52 **Bush G**, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 2000; **4**: 215-222
53 **Ochsner KN**, Ludlow DH, Knierim K, Hanelin J, Ramachandran T, Glover GC, Mackey SC. Neural correlates of individual differences in pain-related fear and anxiety. *Pain* 2006; **120**: 69-77
54 **Naliboff BD**, Mayer EA. Brain imaging in IBS: drawing

the line between cognitive and non-cognitive processes. *Gastroenterology* 2006; **130**: 267-270
55 **Porro CA**, Cettolo V, Francescato MP, Baraldi P. Functional activity mapping of the mesial hemispheric wall during anticipation of pain. *Neuroimage* 2003; **19**: 1738-1747
56 **Yágüez L**, Coen S, Gregory LJ, Amaro E, Altman C, Brammer MJ, Bullmore ET, Williams SC, Aziz Q. Brain response to visceral aversive conditioning: a functional magnetic resonance imaging study. *Gastroenterology* 2005; **128**: 1819-1829
57 **Craig AD**. Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol* 2003; **13**: 500-505
58 **Kringelbach ML**. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci* 2005; **6**: 691-702
59 **Ongür D**, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb Cortex* 2000; **10**: 206-219
60 **Bantick SJ**, Wise RG, Ploghaus A, Clare S, Smith SM, Tracey I. Imaging how attention modulates pain in humans using functional MRI. *Brain* 2002; **125**: 310-319
61 **Ploghaus A**, Becerra L, Borras C, Borsook D. Neural circuitry underlying pain modulation: expectation, hypnosis, placebo. *Trends Cogn Sci* 2003; **7**: 197-200
62 **Frith C**, Dolan R. The role of the prefrontal cortex in higher cognitive functions. *Brain Res Cogn Brain Res* 1996; **5**: 175-181
63 **Fields H**. State-dependent opioid control of pain. *Nat Rev Neurosci* 2004; **5**: 565-575
64 **Rainville P**. Brain mechanisms of pain affect and pain modulation. *Curr Opin Neurobiol* 2002; **12**: 195-204
65 **Millan MJ**. Descending control of pain. *Prog Neurobiol* 2002; **66**: 355-474
66 **Tracey I**, Ploghaus A, Gati JS, Clare S, Smith S, Menon RS, Matthews PM. Imaging attentional modulation of pain in the periaqueductal gray in humans. *J Neurosci* 2002; **22**: 2748-2752
67 **Damasio AR**. Looking for Spinoza: Joy, Sorrow and the Feeling Brain. Orlando: Harcourt, 2003
68 **Damasio AR**, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, Hichwa RD. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat Neurosci* 2000; **3**: 1049-1056
69 **Phillips ML**, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry* 2003; **54**: 504-514
70 **Ekman P**, Friesen WV. Pictures of facial affect. Palo Alto, CA: Consulting Psychologists Press, 1975
71 **Ringel Y**, Drossman DA, Turkington TG, Bradshaw B, Hawk TC, Bangdiwala S, Coleman RE, Whitehead WE. Regional brain activation in response to rectal distension in patients with irritable bowel syndrome and the effect of a history of abuse. *Dig Dis Sci* 2003; **48**: 1774-1781
72 **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
73 **Wilder-Smith CH**, Schindler D, Lovblad K, Redmond SM, Nirkko A. Brain functional magnetic resonance imaging of rectal pain and activation of endogenous inhibitory mechanisms in irritable bowel syndrome patient subgroups and healthy controls. *Gut* 2004; **53**: 1595-1601
74 **Andresen V**, Bach DR, Poellinger A, Tsrouya C, Stroh A, Foerschler A, Georgiewa P, Zimmer C, Mönnikes H. Brain activation responses to subliminal or supraliminal rectal stimuli and to auditory stimuli in irritable bowel syndrome. *Neurogastroenterol Motil* 2005; **17**: 827-837
75 **Kwan CL**, Diamant NE, Pope G, Mikula K, Mikulis DJ, Davis KD. Abnormal forebrain activity in functional bowel disorder patients with chronic pain. *Neurology* 2005; **65**: 1268-1277
76 **Bernstein CN**, Frankenstein UN, Rawsthorne P, Pitz M, Summers R, McIntyre MC. Cortical mapping of visceral pain in patients with GI disorders using functional magnetic resonance imaging. *Am J Gastroenterol* 2002; **97**: 319-327
77 **Chang L**, Mayer EA, Johnson T, FitzGerald LZ, Naliboff B. Differences in somatic perception in female patients with irritable bowel syndrome with and without fibromyalgia. *Pain* 2000; **84**: 297-307
78 **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**: 1187-1192
79 **Verne GN**, Robinson ME, Price DD. Hypersensitivity to visceral and cutaneous pain in the irritable bowel syndrome. *Pain* 2001; **93**: 7-14
80 **Chang L**, Berman S, Mayer EA, Suyenobu B, Derbyshire S, Naliboff B, Vogt B, FitzGerald L, Mandelkern MA. Brain responses to visceral and somatic stimuli in patients with irritable bowel syndrome with and without fibromyalgia. *Am J Gastroenterol* 2003; **98**: 1354-1361
81 **Ringel Y**, Drossman DA, Leserman JN, Lin W, Wilber K, Suyenobu BY, Berman S, William WE, Mayer E. Association between central activation and pain reports in women with IBS. *Gastroenterology* 2006; **130**: A77-A78
82 **Kwan CL**, Diamant NE, Mikula K, Davis KD. Characteristics of rectal perception are altered in irritable bowel syndrome. *Pain* 2005; **113**: 160-171
83 **Lawal A**, Kern M, Sidhu H, Hofmann C, Shaker R. Novel evidence for hypersensitivity of visceral sensory neural circuitry in irritable bowel syndrome patients. *Gastroenterology* 2006; **130**: 26-33
84 **Naliboff BD**, Berman S, Suyenobu B, Labus JS, Chang L, Stains J, Mandelkern MA, Mayer EA. Longitudinal change in perceptual and brain activation response to visceral stimuli in irritable bowel syndrome patients. *Gastroenterology* 2006; **131**: 352-365
85 **Lackner JM**, Lou Coad M, Mertz HR, Wack DS, Katz LA, Krasner SS, Firth R, Mahl TC, Lockwood AH. Cognitive therapy for irritable bowel syndrome is associated with reduced limbic activity, GI symptoms, and anxiety. *Behav Res Ther* 2006; **44**: 621-638
86 **Clouse RE**, Lustman PJ. Use of psychopharmacological agents for functional gastrointestinal disorders. *Gut* 2005; **54**: 1332-1341
87 **Morgan V**, Pickens D, Gautam S, Kessler R, Mertz H. Amitriptyline reduces rectal pain related activation of the anterior cingulate cortex in patients with irritable bowel syndrome. *Gut* 2005; **54**: 601-607
88 **Vandenberghe J**, Dupont P, Persoons P, Demyttenaere K, Tack J. Regional cerebral blood flow during gastric balloon distention in functional dyspepsia. *Gastroenterology* 2003; **124** Suppl 2: A29
89 **Vandenberghe J**, Dupont P, Van Oudenhove L, Bormans G, Demyttenaere K, Fischler B, Geeraerts B, Janssens J, Tack J. Regional cerebral blood flow during gastric balloon distention in functional dyspepsia. *Gastroenterology* 2007; **132**: 1684-1693

S- Editor Liu Y **L- Editor** Alpini GD **E- Editor** Wang HF