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Neuronal correlates of gastric pain induced by fundus distension: a 3T-fMRI study

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Abstract *Visceral hypersensitivity in gastric fundus is a possible pathogenesis for functional dyspepsia. The cortical representation of gastric fundus is still unclear. Growing evidence shows that the insula, but not the primary or secondary somatosensory region (SI or SII), may be the cortical target for visceral pain. Animal studies have also demonstrated that amygdala plays an important role in processing visceral pain. We used fMRI to study central projection of stomach pain from fundus balloon distension. We also tested the hypothesis that there will be neither S1 nor S2 activation, but amygdala activation with the fundus distension. A 3T-fMRI was performed on 10 healthy subjects during baseline, fullness (12.7 ± 0.6 mmHg) and moderate gastric pain (17.0 ± 0.8 mmHg). fMRI signal was modelled by convolving the predetermined psychophysical response. Statistical comparisons were performed between conditions on a group level. Gastric pain activated a wide range of cortical and subcortical structures, including thalamus and insula, anterior and posterior cingulate cortices, basal ganglia, caudate nuclei, amygdala, brain stem, cerebellum and prefrontal cortex ($P < 0.001$). A subset of these neuronal substrates was engaged in the central processing of fullness sensation. SI and SII were not activated during the fundus stimulation. In conclusion, the constellation of neuronal structures activated by fundus distension overlaps the pain matrices induced musculocutaneous pain, with the exception of the absence of SI or SII activation. This may account for the vague nature of visceral sensation/pain. Our data also confirms that the insula and amygdala may act as the central role in visceral sensation/pain, as well as in the proposed sensory-limbic model of learning and memory of pain.*

Keywords *fMRI, functional dyspepsia, gastric fundus, visceral pain.*

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INTRODUCTION

Functional dyspepsia (FD) is a common clinical syndrome diagnosed in nearly one-quarter of all patients with dyspeptic symptoms seen in gastrointestinal (GI) clinics.[1] It is characterized with chronic or recurrent upper abdominal symptoms, such as postprandial epigastric pain, fullness, bloating, nausea and vomiting that cannot be explained by abnormalities on conventional medical investigation. Delayed gastric emptying, impaired gastric fundus accommodation and visceral hypersensitivity has been suggested as the possible pathophysiologies for FD.[2–4] A significant number of FD patients have been found to have visceral hypersensitivity in gastric fundus.[4] In addition to a possible end-organ pathogenesis,[5] abnormal processing of gastric fundus stimuli at the level of the central nervous system can be one of the mechanisms for this visceral hypersensitivity.[6,7] Despite these facts, the brain loci responsible for the pain in gastric fundus remains unclear.

One recent PET study evaluated central processing of gastric pain by gastric 'antrum' balloon stimulation.[8] It revealed significant activation in the thalami, insula bilaterally, anterior cingulate cortex (ACC), caudate nuclei, brain stem, periaqueductal grey matter, cerebellum and occipital cortex, findings that collectively support the notion of a possible common cerebral pain matrix for both somatic and visceral pain. Although being a continuous structure, the fundus and antrum can eventually be viewed as two different organs because they have quite different electrophysiological properties and physiological functions. For example, myocytes in the fundus manifest non-fluctuating transmembrane potential and predominantly exhibit tonic muscular activity, whereas those of the antrum display continuous rhythmic changes in membrane potential (slow waves).[9] The fundus serves as a reservoir, expanding its volume during feeding without changes in wall tension or in intragastric pressure, while the antrum acts primarily in grinding and mixing ingested food.[10] It is not clear whether the gastric fundus and antrum share a similar neural network for processing visceral sensation.

Traditionally, the primary somatosensory region (SI) is involved in the discriminative aspects of somatic sensation.[11] Whether SI is also involved in 'visceral' pain/sensation remains a matter of debate. SI activation has been found during the visceral pain derived from balloon distension in the oesophagus or anorectum,[7,12–20] while not observed in gastric antrum stimulation.[8] The reason for the discrepancy in the central engagement of SI in different parts of the GI tract remains unclear. However, growing evidence from animals and humans suggests that the pathway that provides visceral sensation will go through spinal or vagal afferent system, via thalamus, and finally project to the visceral insular cortex, but not the SI or SII.[21]

The amygdala has been implicated as a key limbic structure involved in anxiety and fear.[22] Amygdala also receives input from brain stem autonomic sensory nuclei (nuclei tractus solitarii, parabrachial nuclei) that are related to visceral sensations, taste, and pain. Considering the interaction among pain sensation, pain unpleasantness, and secondary pain affect, the amygdala is likely to be a neural structure with a role in these dimensions. Several animal studies have also pointed out the crucial role of amygdala in mediating visceral pain.[23–25]

Based on the above description, in the current study, we address the following questions: (i) What cortical and subcortical regions in the human brain are activated by gastric fundus distention (GFD)? (ii) Does the GFD induce SI or SII activation? (iii) Is amygdala activated during the GFD?

MATERIALS AND METHODS

Study population

Ten healthy, right-handed volunteers (eight males, two females; mean age 23.6 years) were studied. The female subjects were tested at their mid-proliferative phase in their menstrual cycle. Written consent for the study was obtained from all participants. The study protocol was approved by the Institutional Ethics and Radiation Safety Committees. No volunteer had a history of diabetes, GI, or neuropsychiatric illness, or was taking medications affecting GI motor function or pain perception. All experiments were conducted in accordance with the Declaration of Helsinki.

Barostat GFD protocols

Subjects fasted overnight. Barostat balloons (1500 mL and 16 cm in maximal volume and diameter, respectively), affixed to double lumen polyvinyl tubes (MUI Scientific, Mississauga, Ontario, Canada), were used for gastric distension. Balloons were passed orally, their position in the gastric fundus was confirmed by fluoroscopy, and tubing was securely taped at the subjects' chins.

Inside the MRI room, the balloon tube was connected via a 5-m extension conduit (polyurethane, internal diameter = 5 mm) to a computer-controlled barostat machine (Distender series II; G&J, Electronics Inc., Willowdale, Ontario, Canada), placed outside the scanning room, for isobaric inflation. The air inflation rate was set to 60 mL s^{-1} throughout the experiment. After an adaptation period, minimal distending pressure (MDP) that allowed recording of breathing-associated changes in intra-abdominal pressure was determined individually in 1-mmHg increments. The MDP (6.1 ± 0.2 mmHg; mean ± SEM) was then used as the baseline throughout the fMRI experiment in order to keep the balloon in place and from complete deflation. MDP distension was subliminal to the subject's conscious awareness.

Before fMRI scanning, the pain threshold was first determined by GFD using an ascending method where 30-s isobaric gastric distensions from the MDP were performed in 2-mmHg increments. The subjects were then instructed to rate their pain intensity using a homemade MRI compatible 100-grade digital visual analogue scale (VAS) meter which was projected onto a screen in the MRI room. The subjects were asked to

score the pain with '0 = no pain' and '100 = the maximum imaginable intensity of pain' during GFD.

Subjects then entered a training session before actual fMRI scanning, aimed to familiarize the subjects with the experiment and to minimize the anxiety that might confound the experiment results. The stimulation pressure was further adjusted according to the individual's psychophysics where VAS was continuously recorded at a 10 Hz sampling rate using an in-house programme. The subjects were given one block of full GFD (to elicit non-painful fullness sensation) and one block of painful GFD (to invoke moderate pain with a VAS rating of 60–70%) each. The stomach was distended in a phasic pattern, and the block lengths were exactly the same as those of the actual fMRI experiment. The actual pressure determined for the subpain threshold stimulus of full GFD was 12.7 ± 0.6 mmHg (threshold-pain pressure minus 2 mmHg), while for the painful GFD was 17.0 ± 0.8 mmHg. The same stimulation parameters were used in the fMRI experiments. Subjects distinguished between fullness and pain sensations clearly without difficulty. As a result of mechanical and perceptual delays, fullness and pain sensation occurred at 8.0 ± 2.0 s and 9.0 ± 1.8 s, respectively, after the onset of GFD stimuli.

For the fMRI study, each session consisted of two blocks of either 40-s painful GFD or full GFD alternating with 40-s baseline (MDP) conditions (Fig. 1). In our pilot psychophysical and fMRI experiments (unpublished data), we observed an overlap in sensations using a more sophisticated design in which all three conditions were randomly distributed in one single session. In this experiment, we adopted a simpler design where only one condition was probed in one fMRI session. The stimulus presentation, controlled by a PC computer, was synchronized with fMRI image acquisition. Each condition was repeated twice, and the test for each individual was completed in 1 day. The order of presentation within and between sessions was balanced among the subjects to minimize the learning, expectation, adaptation and sensitization effects. They were alerted 20–25 s before each fMRI study but were blinded to the distension pressure and paradigm. The subjects' eyes were closed during the experiment. They were instructed to concentrate on the sensation. The subjects reported after the experiment upon enquiry that they could not in any way preconceive or predict the pattern of the stimulation protocol. To avoid the interferences from motor movement and irrelevant cognitive operations, the subjects did not record the VAS during fMRI experiment. The level of sensation was confirmed right after each fMRI study.

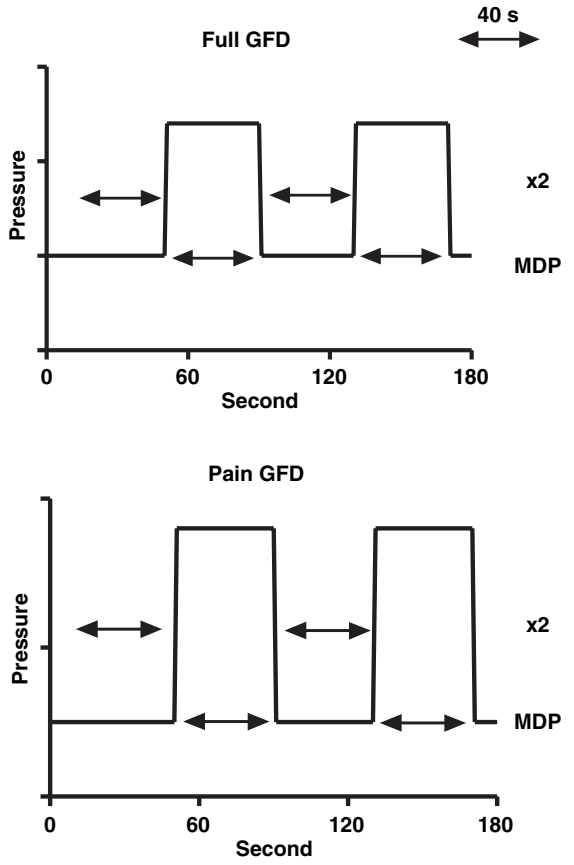

Figure 1 The paradigm of the gastric fundus distention (GFD) in the fMRI study. For each subject, four sessions of either full or painful GFD distension were given. Each session consisted of two blocks of either 40-s painful GFD or full GFD alternating with 40-s baseline condition. Minimal distension pressure (MDP) was served used as a baseline in this study. The order of presentation within and between sessions were balanced among the subjects. They were alerted 20–25 s before each fMRI study but were blinded to the distention pressure and paradigm.

MRI scanning

Images were acquired using a 3.0 T Bruker MedSpec S300 system (Bruker, Kalsrube, Germany) with a quadrature head coil. The subjects' heads were immobilized with a vacuum-beam pad in the scanner. Functional data were acquired with a T2*-weighted gradient-echo EPI using BOLD contrast (TR/TE/θ = 2000 ms/50 ms/90°, slice thickness = 5 mm, interslice interval = 1 mm, Filed of view (FOV) = 250 mm, 64 × 64 × 20 matrix, whole brain coverage). For each slice, 90 images were acquired for every session. The first five images (dummy images) of each session were discarded from the analysis to eliminate possible non-equilibrium effects of magnetization. The

anatomical image was acquired using a high-resolution T1-weighted, 3D gradient-echo pulse sequence [modified driven equilibrium Fourier transform (MDEFT); TR/TE/TI = 88.1 ms/4.12 ms/650 ms, 128 × 128 × 128 matrix, FOV = 250 mm].

fMRI analysis

Data were analysed with statistical parametric mapping (SPM99 software from the Wellcome Department of Cognitive Neurology, London), running under Matlab 6.0 (Mathworks, Sherbon, MA, USA). Scans were realigned, coregistered, normalized, time corrected and spatially smoothed with an 8 mm full-width-at-half-maximum (FWHM) Gaussian kernel using standard SPM methods.[26] The predetermined latencies of perception onset (fullness and pain sensations) relative to the triggering stimuli (full GFD and painful GFD) were respectively incorporated as the regional cerebral blood flow (rCBF) response delay into the two-gamma synthetic haemodynamic response function (HRF) model of SPM99.[27] Contrasts between conditions (pain, fullness sensation) and the corresponding MDP baselines were examined by voxel-specific *t*-tests [SPM (*t*)] across all participants. Comparison between pain and fullness sensation was performed using a fixed-effect analytical approach of SPM99 as pain and fullness were studied on separate fMRI sessions during the experiment where the baseline signals between runs could differ across sessions, albeit the same context of MDP. In brief, the fixed-effect approach took all relevant runs into one single session for modelling and computing the statistics [(pain – corresponding baseline) – (fullness – corresponding baseline)] by treating all conditions as independent.[28] The results by fixed-effect analysis could reveal regions more specifically engaged in the context of gastric pain. The *t*-statistics were subsequently transformed to *Z*-statistics to create a statistical parametric map [SPM (*Z*)] for each contrast. Regionally specific differences surviving an uncorrected threshold of $P = 0.001$ ($Z = 3.10$, cluster size = 5 voxels) were considered statistically significant. *Z*-maxima were localized on the normalized structural image (an SPM99 template) and labelled by means of the Talairach Daemon (Research Imaging Center, The University of Texas, USA).

RESULTS

All subjects endured the GFD procedure well throughout the experiment and experienced distinguishable fullness and pain sensations during the prescanning and scanning experiments.

Effect of full GFD during fullness sensation

Full GFD activated the insula (area 13), superior temporal gyrus (area 22), posterior parietal cortex (PPC; areas 40, 7), prefrontal cortices (PFC; areas 6, 44, 45, 47), and cerebellar hemispheres (Table 1; Fig. 2A). These areas were mainly activated bilaterally. Midline structures, such as the ACC (area 24/31) and PCC (area 29, 30, 31) were also activated with bilateral extension. Activation was also noted in the left side of the occipital cortex (area 18). We did not observe any activation in primary somatosensory (SI, area 1, 2, 3) and secondary somatosensory areas (SII, area 43).

Effect of painful GFD during pain sensation

Most of the involved regions during pain were bilaterally engaged. Structures activated in the fullness sensation were activated also by painful GFD with stronger expression during pain sensation. Painful GFD activated structures of the limbic and paralimbic system, including ACC, PCC, right parahippocampus (area 35) and right amygdala during pain sensation (Table 2; Fig. 2B). Insula (area 13), PFC (area 6, 8, 9, 10, 44, 45, 46, 47) and PPC (area 40,7) were bilaterally activated. The activation loci of ACC (area 24, 32) and PCC (area 23, 29, 31) were in the midline and were spatially extended to the bilateral hemispheres. Thalamus (medial dorsal and ventral posterior lateral nuclei), basal ganglia and caudate nucleus were bilaterally activated. Other activated regions included the cerebellum (vermis), occipital lobe (area 18,19), and brain stem. We observed activation in neither SI nor SII.

The contrast of pain *vs* fullness sensation

Most of the regions activated by painful GFD survived fixed-effect subtraction. The general pattern of the contrast of pain *vs* fullness sensation resembled that of pain *vs* baseline (Table 3; Fig. 2C).

Motor cortex activation

Activation of the primary (area 4) or secondary (area 6) motor cortex was noted in all three conditions (fullness: −30, −20, 40, area 4, $Z = 4.76$; pain: −46, −12, 28, area 6, $Z = 3.30$; pain *vs* full: −32,10,30, area 6, $Z = 3.27$).

DISCUSSION

Our data demonstrates that the central representation for painful GFD involved a wide range of cortical and subcortical structures that comprised a neuronal

Table 1 Foci of activation during fullness

	Left hemisphere					Right hemisphere				
Brain region	Area	*x*	*y*	*z*	*Z*-value	Area	*x*	*y*	*z*	*Z*-value
Frontal lobe										
Inferior frontal G	44,45	−50	18	14	3.83	44,45	58	4	8	7.52
	47	−48	18	−6	5.28	47	52	18	−2	6.18
Middle frontal G	9,10	−40	40	12	3.96	9,10	42	12	38	4.65
Medial frontal G	6	−8	−2	54	6.21	6	6	2	52	4.21
Temporal lobe										
Superior temporal G	22	−54	6	6	4.98	22	48	−14	−2	4.39
						38	42	8	−18	4.01
Parietal lobe										
Inferior parietal L	40	−42	−58	46	3.69	40	50	−44	40	5.11
Precuneus						7	18	−66	34	4.52
Occipital lobe	18	−12	−76	−12	5.27					
Insula	13	−48	16	−4	4.70	13	50	18	0	5.73
Limbic lobe										
Anterior cingulate	32	−2	30	40	3.9					
Posterior cingulate	23,29	0	−42	24	3.57					
Cerebellum										
Anterior L (culmen)		−10	−48	−14	3.87					
Posterior L (declive)		−4	−62	−12	3.26		8	−74	−20	4.56

Steroeotaxic coordinates of peak activation (Talairach & Tournoux, Co-Planar stereotaxic Atlas of the human brain. New York, NY, Thieme, 1988) are expressed in mm and refer to medial-lateral position (*x*) relative to midline (positive = right), anterior-posterior position (*y*) relative to the anterior commissure (positive = anterior), and superior-inferior position (*z*) relative to the commissural plane (positive = superior). G, gyrus; L, lobule; N, nucleus; Inf, *Z*-value > 8.

network (bilateral thalamus, bilateral insula, ACC, PCC, basal ganglia, caudate nuclei, amygdala, brain stem, cerebellum and PFC), overlapping those of cutaneous pain,[11] muscle pain,[29] and gastric antrum distension.[8] A subset of these neuronal substrates serviced the processing of the non-painful stimulation of a similar modality (Tables 1–3; Fig. 2). We also confirmed that SI and SII were not activated during GFD, and amygdala was involved in the processing of visceral sensation.

Traditionally, the principle areas of the brain that participate in the processing of somatic painful responses to noxious stimuli in healthy subjects involve, in general, the lateral pain system (e.g. SI, SII, lateral thalamus) and the medial pain systems (e.g. medial thalamus, ACC and prefrontal cortex).[11] The former, relating the somatosensory cortices, encode the spatial/temporal information, while the latter services the affect-laden responses of pain. In spite of the central representational commonalities with musculocutaneous pain and gastric antral discomfort, there are findings in this visceral pain study that deserve an in-depth discussion.

Little involvement of the lateral pain system: lack of SI and SII activation

The SI and SII are thought to be the two key substrates of the lateral pain system that encode the spatial localization and intensity discrimination of somatic sensation.[11] However, in previous PET/fMRI experiments, the contribution of SI to the processing of somatic pain has been much less consistent across studies than that of SII. Whereas studies from a number of laboratories show that SI is activated during noxious stimuli, others do not report such activation. These controversies are not clear and may be related to the differences in stimuli intensity, type of stimuli, and the spatial or temporal effect of the stimuli.[30] On the contrary, Bushnell *et al.* claimed that the different cognitive modulation in each study, the variability of SI sulcal anatomy among studied subjects, the mixed excitatory and inhibitory effects of nocieceptive input to SI, and different analytic methods through studies may have lead to this controversy.[31] He argued that after correcting for the above mentioned factors, SI cortex plays a prominent and highly modulated role in localization and discrimination of somatic pain.

In the current study, we observed neither activation of SI nor SII under fullness and pain conditions (Tables 1–3). This negative finding is corroborated by a recent PET study on gastric antrum distension.[8] Somatic sensation can be localized precisely, whereas localization of visceral sensation is dull and poorly localized.[32] The perceptual differences possibly reflect differences in the afferent innervations in the end

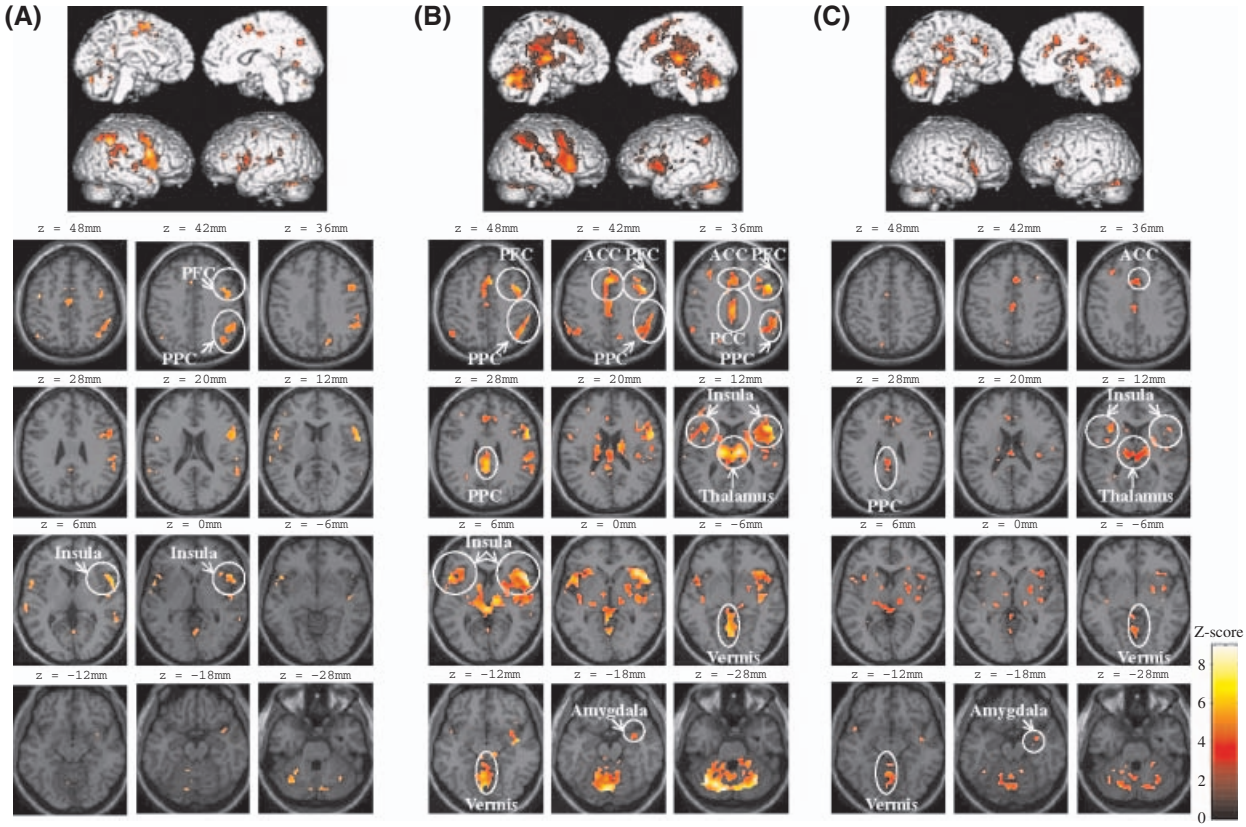

Figure 2 Brain activation in response to balloon distension at gastric fundus. Three columns are shown: (A) full GFD *vs* baseline, (B) painful GFD *vs* baseline, (C) painful GFD *vs* full GFD. Statistical images are coregistered with SPM-MNI template in Talairach space. Rendered views are displayed in the upper panel and a series of axial sections from $z = -28$–50 mm is displayed in the lower panel. The colour bar indicates levels of activation in *Z*-value. *Z*-scores higher than eight are not tabulated. Axial views are displayed according to the neurological convention, i.e. subject's right hemisphere is at the right side of the images.

organs and the pattern of somatic and visceral input to the cerebral cortex.[32] The lack of activation in somatosensory areas in gastric fundus stimulation may account for the ambiguous nature of viscreal pain.[8] Despite this fact, previous studies involving the stimulation in the oesophagus or anorectum have shown activation in SI and SII.[7,12–20] The reason for the discrepancy is unknown. However, it may be the result of the involvement of the somatic component of the oesophagus or anorectum.

Substantial engagement of the medial pain system

It has been previously shown that limbic/paralimbic structures become activated when somatic or visceral sensation is unpleasant or painful.[15,33] The visceral sensation from painful GFD has been also represented in the paralimbic and limbic structures, such as the insular, anterior cingulate, medial thalamus, amygdala and the PFC (Tables 2 and 3; Fig. 2B, C). These areas statistically survived the conservative fixed effect analysis (Table 3) and may mediate the affective and cognitive components of visceral sensation.

Amygdala and temporal lobe

Of note, the right amygdala was activated by painful GFD (Tables 2 and 3; Fig. 2B, C). The activation of amygdala in the current study may echo the aversive and stressful nature of visceral pain. Several animal and human studies have already demonstrated that amygdala plays an important role in mediating visceral pain. For example, noxious colorectal distension has resulted in Fos expression in the amygdala, particularly the central amygdaloid nucleus.[23] A stereotaxic delivery of corticosterone into amygdala can also increase the level of anxiety and produce a hypersensitive colon with hyperactive visceromotor responses.[24] Temporopolar engagement (area 38) in pain processing has been

Table 2 Foci of activation during pain

	Left hemisphere					Right hemisphere				
Brain region	Area	*x*	*y*	*z*	*Z*-value	Area	*x*	*y*	*z*	*Z*-value
Frontal lobe										
Medial frontal G	6	0	−10	64	6.42	6	2	−14	66	5.92
Inferior frontal G	44	−52	4	16	5.15	44	56	6	18	Inf
	47	−34	18	−2	4.04	47	38	22	−2	Inf
Middle frontal G	9,10	−30	30	30	5.38	9,10	46	8	38	Inf
Parietal lobe										
Postcentral gyrus						43	58	−10	18	4.29
Inferior parietal L	40	−56	−50	42	5.10	40	56	−26	26	5.99
Precuneus	7	−20	−60	32	3.81	7	16	−60	42	4.68
Temporal lobe										
Superior temporal G	21,22	−54	6	0	5.59	21,22	44	−6	−10	7.80
	38	−32	6	−22	4.85	38	34	2	−16	5.04
Occipital lobe										
Lingual G	18,19	−2	−72	−8	Inf	18,19	18	−72	−18	Inf
Insula	13	−34	16	8	7.20	13	42	4	6	5.88
Limbic lobe										
Amygdala							30	−8	−18	4.13
Cingulate G	24	−4	2	44	5.20	24	2	−20	36	6.79
	32	0	34	24	5.15	24	2	20	38	7.04
Posterior cingulate	23	0	−26	24	6.56	23	2	−20	36	6.79
	29	−4	−46	4	5.46					
	31	0	−40	26	Inf	31	2	−34	30	7.16
Thalamus										
Medial dorsal N		−6	−20	10	6.68		10	−18	10	Inf
Ventral Post. LN		−12	−16	12	Inf		20	−22	14	6.26
Pulvinar		−2	−28	6	Inf					
Caudate										
Head		−16	−12	20	5.82		16	−6	20	7.21
Lentiform										
Putamen		−22	2	8	3.57		26	−4	10	5.86
Cerebellum										
Anterior L (culmen)		−4	−56	−4	Inf		32	−52	−24	6.10
Vermis		0	−62	0	Inf					
Posterior L (Declive)		−34	−66	−22	Inf		32	−64	−22	Inf
Midbrain		−6	−30	−10	4.49		12	−26	−8	6.84
Pons							14	−34	−24	5.53

Please refer Table 1 for details on steroeotaxic coordinates and other abbreviations.

reported in our previous imaging study on cluster headache.[34] In patients with irritable bowel syndrome (IBS), one researcher found an amygdala deactivation in response to colorectal distension by fMRI.[35] Another recent PET study showed that the amygdala in IBS patients is deactivated after a 5HT3 antagonist, which may be responsible for clinical improvement.[36] All of the above findings agree that the amygdala may play an important role in mediating visceral pain. Our findings may invite further studies to elucidate the role of amygdala with relevance to FD.

Lateralization of amygdala activation in painful GFD is an interesting finding. The literature shows differential function in the left and right amygdala. For example, the right amygdala is dominantly activated in anxiety and anxiety-related physiological responses.[37] Right amygdala, but not left, is mediated by masked (unseen) emotional stimuli.[38] Despite these facts, the functional significance of right amygdala activation is unknown and cannot be determined in our study.

Insula

The insula is the neuronal structure most consistently targeted in pain imaging studies of either a somatic or visceral nature[7,8,12–14,16,20,30,39,40] and has been suggested to be involved in affective-motivational functions, sensory integration and memory of pain.[30] As a result of its connection with many cerebral structures, such as the entorhinal area, hippocampus, amygdala, pre-

Table 3 Foci of activation during pain *vs* fullness

	Left hemisphere					Right hemisphere				
Brain region	Area	*x*	*y*	*z*	*Z*-value	Area	*x*	*y*	*z*	*Z*-value
Frontal lobe										
Inferior frontal G	45	−46	12	8	3.42	44,45	46	18	8	4.13
	47	−44	24	0	3.59	47	42	20	0	4.04
Temporal lobe										
Superior temporal G						21	44	−6	−10	3.98
Fusiform gyrus	37	−38	−58	−20	5.46					
Superior temporal G	38	−48	10	−8	3.84					
Occipital lobe	18,19	−4	−72	−10	5.64	18,19	12	−78	−16	3.66
Insula	13	−34	16	10	6.46	13	46	18	8	4.13
Limbic lobe										
Amygdala							32	−2	−18	4.34
Anterior cingulate G	24	−2	2	44	3.41	24	2	−18	38	4.63
	32	−2	34	22	4.67	32	14	30	24	4.90
Posterior cingulate G	23	0	−18	22	4.22					
	29	−2	−40	20	3.27					
Thalamus										
Dorsal medial N		−12	−18	12	4.77		14	−14	12	4.93
Ventral posterior LN		−20	−22	2	4.22		18	−20	2	4.1
Pulvinar		−2	−26	6	4.49		4	−28	6	4.81
Caudate										
Body		−16	−14	22	3.69		16	−4	22	3.92
Lentiform										
Lateral globus pallidus							24	−4	−4	4.08
Putamen							28	−4	12	4.60
Claustrum		−38	−20	−2	3.40		38	−14	4	4.54
Cerebellum										
Anterior L (Culmen)		−2	−54	−8	6.46		32	−58	−24	5.13
Vermis		0	−60	0	5.11					
Posterior L (Declive)		−20	−68	−18	6.08		16	−68	−18	5

Please refer Table 1 for details on steroeotaxic coordinates and other abbreviations.

frontal cortex, motor/premotor cortex and basal ganglia, the insula cortex (particularly anterior insula) has been suggested as a multifaceted-sensory area and functions as a critical integration cortex, servicing visceral sensation, visceral motor control, motor association, and emotional response to distressing cognitive or interoceptive sensory stimuli.[41] We observed a bilateral engagement of the anterior insula (area 13) in fullness and pain conditions (Tables 1–3). The anterior insula manifests the region of highest Z_{max} (fixed effect analysis) in the cerebrum (Table 3). It is temping to speculate that the insula may be the primary cortical target of the visceral afferents from the gastric fundus. This point is further augmented by two recent reviews from Saper and Craig, both raising the point that the insula is the final common target of both sympathetic and parasympathetic afferents.[21,42]

Studies from primates, including humans, have already shown that there exists a topographic ordering of visceral sensation.[41,43] When compared with other functional brain imaging studies of visceral pain, we further found that the activated loci of gastric representation in the insula were located clustered in a position higher (*z*-coordinates) than other parts of the gut (Table 4). The findings of viscerotopical organization in the insula of rats raise the possibility of a similar viscerotopical representation in the insula of humans.[44]

Thalamus

Painful GFD produced robust bilateral thalamic activation (Tables 2 and 3; Fig. 2B, C), similar to the reported unpleasant colorectal distension,[7] painful antrum distension,[8] and angina.[45] The thalamus relays peripheral input with the cerebral cortex and basal ganglion (see below). Although the resolution limit precluded a precise identification of thalamic subnuclei involved, the peak activations were centred in the regions of the right and left dorsomedial and ventral posterolateral nuclei (VPL). The former is part of a medial pain system linking projection to ACC, while the latter is one key component of the lateral pain

Table 4 Summary of loci of insula activation from the literature on visceral sensation

					Left insula			Right insula		
Location	References	Method	Condition	Side(s)	*x*	*y*	*z*	*x*	*y*	*z*
Oesophagus	Aziz[12]	PET	Balloon							
			Non-painful	Bil.	−27	10	1	NA	NA	NA
			Pain	Bil.	NA	NA	NA	NA	NA	NA
			Pain *vs* sensation	Right				31	30	−6
	Binkofski[15]	fMRI	Balloon (pressure sensation)	Bil.	−42	12	−6	40	12	−6
	Kern[16]	fMRI	Balloon (subliminal)	Bil.	NA	NA	NA	NA	NA	NA
			Acid (subliminal)	Bil.	NA	NA	NA	NA	NA	NA
	Aziz[13]	fMRI	Balloon proximal (non-painful)	Right				43	−3	−2
			Balloon distal (non-painful)	Right				46	−14	−2
Averaged coordinates					**−31**	**11**	**−2**	**40**	**6**	**−4**
Anorectum	Silverman[20]	PET	Balloon, rectum (pain)	Nil						
	Baciu[14]	fMRI	Balloon, rectum (pain)	Bil.	NA	NA	NA	NA	NA	NA
	Mertz[7]	fMRI	Balloon, rectum (pain)	Bil.	NA	NA	NA	NA	NA	NA
	Lotze[18]	fMRI	Balloon, anus (non-painful)	Bil.	−51	6	3	45	9	0
			Balloon, rectum (non-painful)	Bil.	−39	12	0	36	21	−3
			Balloon, anus *vs* rectum	Nil			-			
	Hobday[19]	fMRI	Balloon, anus (non-painful)	Bil.	−40	4	0	40	4	0
			Balloon, rectum (non-painful)	Bil.	−50	5	3	50	5	3
	Kern[17]*	fMRI	Balloon, rectum, male	Nil						
			Balloon, rectum, female							
			Subliminal	Bil.	−42	12	−1	34	13	−1
			Liminal	Bil.	−41	16	0	35	23	0
			Supraliminal	Bil.	−41	16	0	35	23	3
Averaged coordinates					**−43**	**10**	**1**	**39**	**14**	**0**
Stomach	Ladabaum[8]	PET	Balloon, antrum, mild pain	Bil.	−33	8	14	33	3	11
			Balloon, antrum, moderate pain	Bil.	−35	8	7	39	8	7
	Lu (unpublished)	fMRI	Balloon, fundus, fullness	Bil.	−48	16	−4	50	18	0
			Ballon, fundus, pain	Bil.	−34	16	8	42	4	6
			Ballon, fundus, pain	Bil.	−34	16	10	46	18	8
Averaged coordinates					**−37**	**13**	**7**	**42**	**10**	**6**

Bil., bilateral; NA, not available; *The coordinates obtained in this study were from the average of the studied subjects.

system.[16] It is noteworthy that in somatic pain studies, the activation of thalamus, particularly VPL, is usually coupled with SII and/or SI activation.[30] In our study, the VPL activation was without concomitant engagement in the somatosensory area. This can be explained by the different pathways between somatic and visceral pain. Evidence has shown that the visceral sensory pathway is to the thalamus, and is composed both of sympathetic and parasympathetic afferent.[21] The vagal afferents relay in the medial thalamus and project to the anterior insula cortex, while the spinal visceral afferents relay in the VPL and then are projected more caudally in the insula area.

Anterior cingulate cortex and posterior cingulate cortex

The ACC activation is located at the midrostrocaudal portion (areas 24, 32). Similar to the insula, this part of the ACC is also one of the structures most consistently activated in somatic and visceral pain imaging studies.[7,8,12–14,16,17,33] A large body of evidence suggests that the ACC filters and controls the relationship between the emotional limbic system and the skeletomotor and autonomic part of the nervous system, and endocrine function, which in turn regulates the internal emotional responses and motivational reactions, which in turn pertains to the organization of an appropriate response to pain.[46]

The PCC activation by painful GFD peaked in the anterior segment (area 23) and spatially extended to the posterior segment (retrosplenial cortex, areas 29/30, 31) (Table 2; Fig. 2B). The activation survived conservative fixed-effect analysis (Table 3; Fig. 2C). The PCC activation has been reported with oesophageal acid and balloon stimulation,[16] rectal stimulation,[14] and angina attack.[45] Its relation to pain has been less explored. The activated anterior PCC encompasses a spatial region

that in monkeys receives nociceptive inputs from posterior thalamic medial/lateral nuclei, which in turn are targets for spinothalamic terminations,[47] and which has been proposed as a specific pain area in the PCC of humans.[48] The posterior PCC (retrosplenial cortex), the most caudal region of the cingulate cortex, is largely devoid of primary motor and sensory inputs, and receives major inputs from the orbital and dorsolateral prefrontal cortex, the ACC, parahippocampal cortex, superior temporal sulcus, precuneus, claustrum, and the anterior and lateral thalamic nuclei.[49] This PCC cortical region is the structure most consistently and specifically activated by emotional salience of stimuli and has been suggested to participate in the interaction between emotion and episodic memory.[49] Evidence for these functional properties led to the hypothesis that anchors the functions of the PCC as 'evaluative' in contrast to the 'executive' functions of ACC.[50] Many of the aforementioned structures were discretely activated by painful GFD in this study (Tables 2 and 3; Fig. 2B, C). It has been suggested that ACC, PCC, PPC and the medial parietal cortex (precuneus, area 7) are key substrates in re-mapping the bodily representation of the organism in response to current behavioural experiences and environmental contexts, drawing on representations of salient stimuli and events, and subserve emotions and conscious awareness.[51]

Findings from available studies on patients with functional GI disorders, however, have not been uniform and are not always in agreement. Both failure of activation and exaggerated activity of the cingulate cortex (i.e. ACC) in response to balloon distension have been reported in patients with IBS.[7,20] It remains to be explored whether patients with FD demonstrate aberrant cortical activation in the ACC and PCC upon gastric distension compared with controls.

Caudate nucleus and basal ganglia

Similar to the study on gastric antrum distension,[8] we also observed a prominent activation in the bilateral basal ganglia (lentiform nuclei, Tables 2 and 3) and caudate nuclei. It has been suggested that neurones of the caudate nucleus play a role in the mechanisms of interaction of visceral impulses with somatic and auditory impulses.[52] Basal ganglia may integrate multiple sensory modalities and coordinate behavioural responses because it receives convergent input from olfactory, auditory and somatosensory sources in addition to the important role in motor processes.[53] There is evidence that basal ganglia is involved in the multidimensionality of pain, modulation of the nociceptive information, and sensory gating of nociceptive information to higher motor areas for response planning.[53] It can be speculated that the activation of caudate and basal ganglia, perhaps in association with supplementary motor areas (area 6) as well, might effectuate the networking of poorly localized internal and unpleasant sensations with visceromotor reactions in response to GFD-induced abdominal pain.

Cerebellum and brain stem

The loci of activation in the cerebellum (Tables 2 and 3) coincide with those of cutaneous and muscular pain.[29] Animal studies have revealed that the cerebellum and structures of the brain stem are involved in visceral nociceptive processing.[54] The cerebellum may not directly mediate the perception of sensation. Instead, it can be an important substrate in integral sensorimotor circuitry, encompassing spinocerebellar and vestibulocerebellar pathways,[55] and services in part, the over motor planning in response to the noxious stimulation and participates in the modulation and coordination of a wide range of central nervous activities, somatic and non-somatic.[56]

Prefrontal cortex and posterior parietal cortex

Participation of these regions in both attention and executive functions is well known, their activation being frequently described in experiments involving attention, working memory and goal-directed processes.[57] PFC and PPC responses (Tables 2 and 3; Fig. 2B) observed in our study and other pain imaging studies have been repeatedly reported as 'pain-related' activities and have been suggested to mediate part of the cognitive dimension of pain processing associated with sensory gating,[58] localization and encoding of the attended stimulus.[11,30] Although bilateral, these cortical activities often show asymmetrical distribution and predominate on the right hemisphere (also shown in Tables 2 and 3; Fig. 2B) in attention-loaded sensory experiments.[30,59] Our data imply that similar mechanisms are engaged in the appreciation of the interoceptive experience.

Motor cortex activation

Activation in the motor and motor-associated region was also noted during fundus stimulation. The reason for this observation is unclear, but similar findings have been reported in other visceral organ (oesophagus).[17,18] The activated motor area was mainly the control in the facial, masticatory and pharyngeal muscle. Hence, this might be the result of the effect

of our intubated balloon catheter or a non-specific motor response to pain.

Comments on the method

Caution should be exercised in the interpretation of the current results because male predominated in the studied subjects as a result of the difficulty in recruiting female volunteers. Gender differences in the expression of the pain matrix have been reported on both cutaneous pain[60] and visceral pain induced by rectal distention.[17] Male subjects showed localized clusters of activity primarily in the sensory and parietooccipital regions, whereas female subjects showed more expressed activity in the ACC, insula and thalamus.[17] Furthermore, the study subjects experienced both non-painful and painful GFD in the preparatory phase, so it may have induced an anticipation of painful distension, even when that was not employed. This made us to be cautious in the interpretation of the activation of ACC and PFC during the full GFD, activation of which might be the result of the anticipation of pain rather than the actual pain *per se*. Although MDP used in this study was subliminal to subjects' conscious awareness, it has been demonstrated that subliminal afferent signals originating from the lower gut are registered in the cerebral cortex and induces detectable changes in fMRI measures of brain activity.[61] Further study is needed to clarify the issue of gastric subliminal stimulation.

In conclusion, we report that gastric pain induced by GFD is represented in the paralimbic and limbic structures, and also many other structures of the brain, in a manner similar to that of somatic and gastric antrum sensation. The constellation of activation in these neuronal structures partially overlaps the pain matrices as disclosed by experimentally induced musculocutaneous and other types of visceral pain. Lack of significant activation in somatosensory areas in this study of gastric pain may account for the ambiguous nature of visceral pain. The current data emphasize that the connections with the insula may be more cardinal than the networking with the superficial parietal operculum (e.g. SII) for visceral sensation. Studies on factors that modulate the brain processing of gastric pain in healthy and diseased subjects are currently being undertaken to better elucidate the pathophysiology of functional GI disorders.

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