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Cortical deactivations during gastric fundus distension in health: visceral pain-specific response or attenuation of 'default mode' brain function? A $H_2{}^{15}O$-PET study

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Abstract *Gastric distension activates a cerebral network including brainstem, thalamus, insula, perigenual anterior cingulate, cerebellum, ventrolateral prefrontal cortex and potentially somatosensory regions. Cortical deactivations during gastric distension have hardly been reported. To describe brain areas of decreased activity during gastric fundus distension compared to baseline, using data from our previously published study (Gastroenterology, 128, 2005 and 564). $H_2{}^{15}O$-brain positron emission tomography was performed in 11 healthy volunteers during five conditions (random order): (C_1) no distension (baseline); isobaric distension to individual thresholds for (C_2) first, (C_3) marked, (C_4) unpleasant sensation and (C_5) sham distension. Subtraction analyses were performed (in SPM2) to determine deactivated areas during distension compared to baseline, with a threshold of $P_{uncorrected\_voxel\_level} < 0.001$ and $P_{corrected\_cluster\_level} < 0.05$. Baseline–maximal distension (C_1–C_4) yielded significant deactivations in: (i) bilateral occipital, lateral parietal and temporal cortex as well as medial parietal lobe (posterior cingulate and precuneus) and medial temporal lobe (hippocampus and amygdala), (ii) right dorsolateral and dorso- and ventromedial PFC, (iii) left subgenual ACC and bilateral caudate head. Intragastric pressure and epigastric sensation score correlated negatively with brain activity in similar regions. The right hippocampus/amygdala deactivation was specific to sham. Gastric fundus distension in health is associated with extensive cortical deactivations, besides the activations described before. Whether this represents task-independent suspension of 'default mode' activity (as described in various cognitive tasks) or an visceral pain/interoception-specific process remains to be elucidated.*

Keywords *central nervous system, cortical deactivations, functional brain imaging, gastric fundus distension, interoception.*

Abbreviations: (s/p)ACC, (subgenual/perigenual) anterior cingulate cortex; (vl/vm/dm/dl) PFC, (ventrolateral/ventromedial/dorsomedial/dorsolateral) prefrontal cortex;(m/l) OFC, (medial/lateral) orbitofrontal cortex; BA, Brodmann Area; PET, positron emission tomography; SI/SII, primary & secondary somatosensory cortex; PCC, posterior cingulate cortex; PAG, periaqueductal gray; IBS, irritable bowel syndrome.

INTRODUCTION

Painful gastric distension is processed in a network consisting of brainstem, thalamus, insula, perigenual

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anterior cingulate cortex (pACC), ventrolateral prefrontal cortex (vlPFC), temporal cortex and cerebellum.[1–6] The role of primary and secondary somatosensory cortex (SI/SII) in the processing of gastric distension is controversial, with conflicting results in different studies.[2–4,6–8] Compared to literature on cortical activation, evidence on reduced brain activity during noxious visceral distension in general and gastric distension in particular, is relatively sparse. However, cortical deactivations were reported during oesophageal[9] and rectal balloon distension[10–13] in health and disease. These deactivations were mainly located in occipital, posterior parietal and prefrontal areas.

Ladabaum *et al.* studied regional brain activity during distal gastric (antral) balloon distension using positron emission tomography (PET) and reported decreases in blood flow in ventromedial (vm)PFC, subgenual (s)ACC, posterior cingulate cortex (PCC), parahippocampal gyrus and occipital cortex during distension compared to baseline.[5] However, the relevance or interpretation of these deactivations are hardly discussed. Cortical deactivations are more frequently found in brain imaging studies using physiologic methods of gastric distension, for example nutrient infusion. Nutrient liquid meal ingestion until satiation after a 36-h fast has been associated with deactivations in widespread cortical areas, including medial temporal areas (parahippocampal gyrus, hippocampus and amygdala), striatum, precuneus and insula,[14,15] although these studies may be difficult to compare with balloon distension studies. A preliminary report by our group showed deactivations in SII and insular cortex after intragastric infusion of a liquid meal until discomfort, compared to baseline.[16]

In somatic pain, finally, deactivations in dorsolateral (dl)PFC and vmPFC, sACC, posterior parietal, temporal and occipital areas and right hippocampus have been described,[17–24] as well as a decrease in regional activity in contralateral SI[25] and a 'global decrease in cerebral blood flow'.[26] Deactivation of the amygdala during somatic pain has been reported and may represent an adaptive response to an unavoidable painful stimulus, thereby attenuating pain-related stress-responses.[27]

To the best of our knowledge, cortical deactivations during balloon distension of the proximal stomach (fundus) have not been reported. We therefore re-analyzed the data from our previously published PET-study in healthy volunteers,[3] looking for potential deactivations during fundus distension compared to baseline. The activations found in this study have been previously reported.[3]

The rationale for the present report was twofold. First, recent data have pointed to a 'default mode' brain function during 'rest' or 'baseline', which is disrupted during various attention-demanding (cognitive-perceptual) tasks, causing largely task-independent deactivations, compared to the 'default mode' baseline state. The deactivations during the above tasks are located mainly in lateral and medial (precuneus and adjacent PCC) parietal cortex, medial prefrontal areas and adjacent ACC and medial temporal lobe [amygdala, (para)hippocampus].[28–34] The 'default mode' brain network has been hypothesized to be active during rest (i.e. when the individual is not focused on any particular aspect of the environment), with a putative role in 'internal cognition' and/or scanning of the external environment in the absence of attention-demanding stimuli.[30,35,36] Second, the present analysis was motivated by the limited evidence of similar deactivations in the visceral and somatic sensory literature described above.

METHODS

Subjects

Eleven healthy and asymptomatic subjects (five men and six women; mean age, 23.1 ± 1.7 years) who were not taking any medication and who had no history of gastrointestinal, neurological or psychiatric disease participated in the study. All volunteers recruited completed the study as planned. All volunteers studied had previous experience with barostat studies, but none of them had undergone a PET brain imaging study before. All study procedures were undertaken with the understanding of and after obtaining written consent from each subject, in accordance with the Declaration of Human Rights (World Medical Association Declaration of Helsinki, 1975).[37] The protocol had been approved by the ethical committee of the University Hospital prior to the start of the study.

Barostat procedure

The protocol has been previously described in detail.[3,38,39] Briefly, to assess individual perception thresholds, isobaric distentions were performed in double random staircase increments of 2 mmHg starting from minimal distending pressure, each lasting for 2 min, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper abdominal sensations at the end of every distending step using a graphic rating scale that combined verbal descriptors on a scale graded 0–6 (0 = no sensation, 1 = weak sensation, 2 = moderate

sensation, 3 = marked sensation, 4 = pronounced sensation, 5 = unpleasant sensation/discomfort and 6 = pain), as previously reported.[3,38–42] The end point of each sequence of distentions was established when the subjects reported discomfort or pain (score 5 or 6). From these ratings during the double random staircase distentions, we obtained the individual's pressure thresholds for first perception (mean pressure inducing score 1 or higher), marked perception (mean pressure inducing score 3 or higher) and unpleasant or painful sensation (mean pressure inducing score 5 or higher). For most of the subjects, we were able to obtain pain thresholds during distension; in that case these were used during scanning. In some subjects, however, the distension had to be stopped due to intolerable discomfort without reaching pain; in these cases, discomfort thresholds were used.

PET imaging

As the protocol has been described in detail previously,[3] we will only provide a short summary here.

Conditions Brain $H_2{}^{15}O$-PET was performed during four conditions: (C_1) no distension ('baseline') and distension to the individual thresholds for (C_2) weak/first, (C_3) marked and (C_4) unpleasant or painful sensation as determined in the preceding barostat procedure. To control for anticipation, a sham condition (C_5) was included, during which distension was anticipated but not actually delivered (i.e. the subject was informed that a distension would take place during the following scan, but no distension was delivered). During all conditions, subjects were instructed to lie quietly with their eyes open as this may be the closest approximation of a true 'baseline state'.[28] Therefore, and given the fact that this is a PET-study, the baseline condition may represent a true 'physiologic baseline' reflecting a coherent set of processes, known as 'default mode' of brain function.[28,30–34] Each condition was replicated three times in a pseudo-randomized block design. Gastric sensation was rated with the same 0–6 graded graphic rating scale immediately after each distension. Pain, discomfort, nausea, and bloating during the most intense distension were rated on a visual analogue scale immediately after the entire scanning session.

Data acquisition One minute after starting intragastric balloon inflation (if applicable), intravenous injection of 300 MBq $H_2{}^{15}O$ was administered over 12 s, with a 12-min interval between successive injections to allow for radiotracer decay. Data acquisition (60 s) began as the intracranial radioactivity count rate increased sharply (40–60 s after start of the injection). The intragastric balloon was deflated immediately after completion of data acquisition. It was kept deflated in-between periods of data acquisition.

Data analysis Brain imaging data were analyzed using statistical parametric mapping (SPM2; Wellcome Department of Cognitive Neurology; http://www.fil.ion.ucl.ac.uk/spm). Preprocessing steps are: correction for small movements, warping to Montreal Neurological Institute (MNI) space and smoothing the images with a three-dimensional isotropic Gaussian kernel of 16 mm full width half maximum. A brain mask was used to eliminate extracerebral activity. Condition and covariate effects were estimated according to the general linear model at each voxel, with proportional scaling as global normalization method.

Contrasts To determine deactivations in the distension conditions relative to the baseline, activity in the respective distension condition was subtracted from activity in the baseline condition. As maximal effects were anticipated, the main analysis focused on baseline-painful sensation ($C_1 - C_4$), but also the marked and first sensation conditions were subtracted from baseline ($C_1 - C_3$ and $C_1 - C_2$, respectively).

Correlation analyses between intragastric pressure and gastric sensation score on the one hand and brain activation on the other were also performed. Intragastric pressure was continuously recorded during scanning, using the computer-controlled barostat device. We used the main intragastric pressure during the period of scanning to correlate with brain activity. Intragastric pressure or gastric sensation were entered as independent variable (one value per scan), and their interaction with subject.

To determine anticipation (sham)-specific deactivations, sham activity was subtracted from baseline activity ($C_1 - C_5$).

To determine pain-specific deactivations (i.e. regions deactivated during pain compared to first or marked sensation), activity during painful sensation was subtracted from activity during weak/first and marked sensation ($C_2 - C_4$ and $C_3 - C_4$).

All analyses were done at the whole brain-level, without *a priori* defined regions of interest, given the rather exploratory nature of the study due to the sparsity of literature on cortical deactivations during gastric distension. As in our previously published study reporting on activations in the same subject sample,[3] for all analyses, significance threshold was set

at voxel level of $P_{uncorrected} < 0.001$, with an extent threshold of 20 voxels (0.16 cm^3). However, to reduce false-positive findings we considered only those clusters reaching significance at the $P_{corrected} < 0.05$ cluster level (correction for multiple comparisons) in the main subtraction analysis. Within each cluster, only local maxima more than 1 cm apart are shown.

Anatomic magnetic resonance imaging data Each subject underwent a high-resolution MRI scan for coregistration with PET images as previously described.[3,43]

RESULTS

Behavioural

The numerical details on thresholds, ratings and VAS scores have been published in our previous study on the same subject sample.[3]

Baseline – unpleasant/painful sensation ($C_1 - C_4$)

Significant deactivations during distension at individually determined discomfort threshold compared to baseline are shown in Table 1 and Figs 1 and 2. The deactivated network consists of occipital and adjacent lateral parietal and temporal cortex, medial parietal cortex (posterior cingulate cortex and adjacent precuneus), medial temporal lobe (hippocampus and amygdala), medial prefrontal cortex and subgenual anterior cingulate.

Baseline – marked sensation ($C_1 - C_3$)

This subtraction yielded a pattern of deactivations that was similar to the $C_1 - C_4$ contrast, although less extensive, as can be seen in Table 2 and Fig. 3. Deactivations were mainly found in occipital, parietal and medial temporal areas, as well as, though to a lesser extent, medial prefrontal cortex. It should be noted that in this contrast, the subgenual anterior cingulate/caudate head cluster was only significant at the voxel level of $P_{uncorrected} < 0.001$, not at the cluster level of $P_{FWE\text{-}corrected} < 0.05$ (MNI-coordinates 8,12,−8, $t = 4.04$, $k = 222$, BA 25).

Baseline – weak/first sensation ($C_1 - C_2$)

Clusters that were significantly deactivated during first sensation compared to baseline, at the voxel level of $P_{uncorrected} < 0.001$ are shown in Fig. 3. None of these clusters reached significance at the cluster level of $P_{FWE\text{-}corrected} < 0.05$. These clusters are located in left lingual/fusiform gyrus (including part of the anterior cerebellum and hippocampus; MNI-coordinates −18,−34,−24 and −18,−42,−6, $t = 4.12$ & 3.79, $k = 515$, BA 37/30), right middle temporal/occipital gyrus (MNI-coordinates 40,−68,20 & 36,−82,24, $t = 3.81$ & 3.25, $k = 186$, BA 39/19), left lingual/inferior occipital gyrus (MNI-coordinates −18,−86,−14 & −14,−96,−8, $t = 3.47$ & 3.21, $k = 118$, BA 17/18), left precuneus (MNI-coordinates −2,−56,62, $t = 3.34$, $k = 103$, BA 7/5), right supramarginal gyrus (MNI-coordinates 48,−38,26, $t = 3.53$, $k = 57$, BA 41), right temporal pole (MNI-coordinates 34,22,−32, $t = 3.88$, $k = 101$, BA 38), left medial frontal gyrus (MNI-coordinates −2,60,12, $t = 3.44$, $k = 65$, BA 10) and left subgenual anterior cingulate cortex (sACC; MNI-coordinates −4,28,−2, $t = 3.47$, $k = 33$, BA 25).

Correlation analyses

When intragastric pressure or gastric sensation score were correlated with brain activation, negative correlations were found with regions found to be deactivated during distension. The results were very similar to the result from the main subtraction analysis $C_1 - C_4$ (Table 1), in terms of significance and localization of the local maxima. Details are listed in two Supporting information tables.

Baseline – sham ($C_1 - C_5$)

The following cluster were significantly deactivated during sham compared to baseline, at the voxel level of $P_{uncorrected} < 0.001$ and $P_{FWE\text{-}corrected} < 0.05$ (cluster level): right amygdala/hippocampus and adjacent medial temporal pole [MNI-coordinates of local maxima 26,−8,−30 and 38,18,−34, $t = 4.82$ and 3.53, $k = 626$, $P_{FWE\text{-}corrected} = 0.05$ (cluster level)].

Weak/first sensation – unpleasant/painful sensation ($C_2 - C_4$)

The results of this subtraction are listed in Table 3. Deactivations were found in occipital, (mostly medial) parietal and medial temporal lobes. No prefrontal or cingulate deactivations were observed.

Marked sensation – unpleasant/painful sensation ($C_3 - C_4$)

The following clusters were significantly deactivated, at the voxel level of $P_{uncorrected} < 0.001$: left inferior temporal gyrus (MNI-coordinates −56, −28, −26,

Table 1 Deactivations during gastric fundic distension at individually determined discomfort threshold (unpleasant/painful sensation) compared to baseline (C_1–C_4)

MNI-coordinate local max x,y,z (mm)	Tentative anatomical localization	*t*-value (voxel level)	$P_{FDR\text{-corrected}}$ (voxel level)	$P_{FWE\text{-corrected}}$ (voxel level	No. voxels	P_{corr} (cluster level)
34,−80,24	Right middle temporal gyrus middle occipital gyrus (BA 19)	7.40	<0.001	<0.001	51 767	<0.001
−14,−76,−2	Left occipito-temporal lobe: lingual gyrus (BA 18)	6.13	<0.001	<0.001		
42,−32,−26	Right occipito-temporal lobe: fusiform gyrus (BA 20)	6.07	<0.001	<0.001		
−32,−22,−20	Left hippocampus, includes amygdala	5.98	<0.001	<0.001		
48,−62,−6	Right inferior temporal gyrus/middle occipital gyrus	5.85	<0.001	<0.001		
24,−16,−24	Right hippocampus, includes amygdala	5.76	<0.001	<0.001		
−40,−76,−6	Left inferior occipital gyrus (BA 19)	5.66	<0.001	0.001		
24,−30,−20	Right temporal lobe: fusiform-parahippocampal gyrus (BA 20, 30, 36)	5.52	<0.001	0.001		
−26,−78,38	Left middle occipital gyrus (BA 19)	5.48	<0.001	0.001		
−20,−50,−8	Left temporo-occipital lobe: lingual/fusiform gyrus (BA 37/19)	5.46	<0.001	0.002		
52,−40,22	Right superior temporal gyrus/inferior parietal lobule (BA 41,42/40)	5.46	<0.001	0.002		
−54,−62,−10	Left middle occipital gyrus/inferior temporal gyrus (BA 37)	5.38	<0.001	0.002		
6,−76,46	Right parietal lobe: precuneus (BA 7)	5.33	<0.001	0.003		
48,−8,−22	Right occipito-temporal lobe: fusiform gyrus (BA 20)	5.32	<0.001	0.003		
0,−52,50	Midline parietal lobe: precuneus (BA 7) includes PCC (BA 23, 30, 31)	5.26	<0.001	0.004		
−46,−70,14	Left middle temporal gyrus	5.11	<0.001	0.006		
4,−66,12	Right occipital lobe: calcarine gyrus(BA 17, 18)	4.89	<0.001	0.018		
38,2,48	Right frontal lobe: precentral/middle frontal gyrus (BA 6)	4.80	<0.001	0.020		
32,4,60	Right middle frontal gyrus (BA 6, 8)	4.74	<0.001	0.025		
18,−64,0	Right occipital lobe: lingual gyrus,cuneus (BA 17,18,19)	4.64	<0.001	0.036		
34,−12,54	Right precentral gyrus (BA 6)	4.64	<0.001	0.036		
6,−52,4	Right occipital lobe: lingual gyrus (BA 18)	4.52	<0.001	0.054		
52,22,22	Right inferior frontal gyrus (pars triangularis) (BA 45)	4.51	<0.001	0.056		
36,−54,56	Right superior parietal lobule (BA 7, 40)	4.48	<0.001	0.061		
30,30,42	Right middle frontal gyrus (BA 9: dlPFC)	4.38	<0.001	0.086		
44,−34,54	Right postcentral gyrus (BA 1, 2)	4.26	<0.001	0.124		
−42,−32,42	Left postcentral gyrus (BA 2)	4.08	<0.001	0.210		
−56,−10,−12	Left inferior/middle temporal gyrus (BA 21, 22)	3.97	0.001	0.286		
−28,8,−36	Left superior temporal gyrus (medial temporal pole, BA 38)	3.95	0.001	0.302		
28,14,−36	Right superior temporal gyrus (medial temporal pole, BA 38)	3.75	0.001	0.471		
−36,−40,56	Left postcentral gyrus (BA 2, 1, 3b)	3.57	0.002	0.650		
−2,−22,−70	Left middle frontal gyrus/paracentral lobule (BA 6, 4a)	3.43	0.002	0.787		
12,50,34	Right superior/medial frontal gyrus (BA 9, dmPFC)	4.60	<0.001	0.040	2217	<0.001
6,66,0	Right superior/medial frontal gyrus (BA 10, vmPFC)	4.34	<0.001	0.096		
0,56,12	Right medial frontal gyrus (BA 10, vmPFC)	4.10	<0.001	0.201		
8,16,−6	Right caudate head/sACC (BA 25)	4.36	<0.001	0.091	1289	0.005
−6,24,−8	Left sACC (BA 25)	4.10	<0.001	0.201		
−12,18,0	Left caudate head	3.79	<0.001	0.433		
−36,0,56	Left precentral gyrus (BA 6)	4.51	<0.001	0.055	647	0.049

Significance threshold was set at $P_{uncorrected} < 0.001$ (voxel level); only clusters reaching significance at $P_{corrected} < 0.05$ (cluster level) were included in the table. Within each cluster, only local maxima more than 1 cm apart are shown.
BA, Brodmann Area; (dl/dm/vm)PFC, (dorsolateral/dorsomedial/ventromedial) prefrontal cortex; PCC, posterior cingulate cortex; sACC, subgenual anterior cingulate cortex.

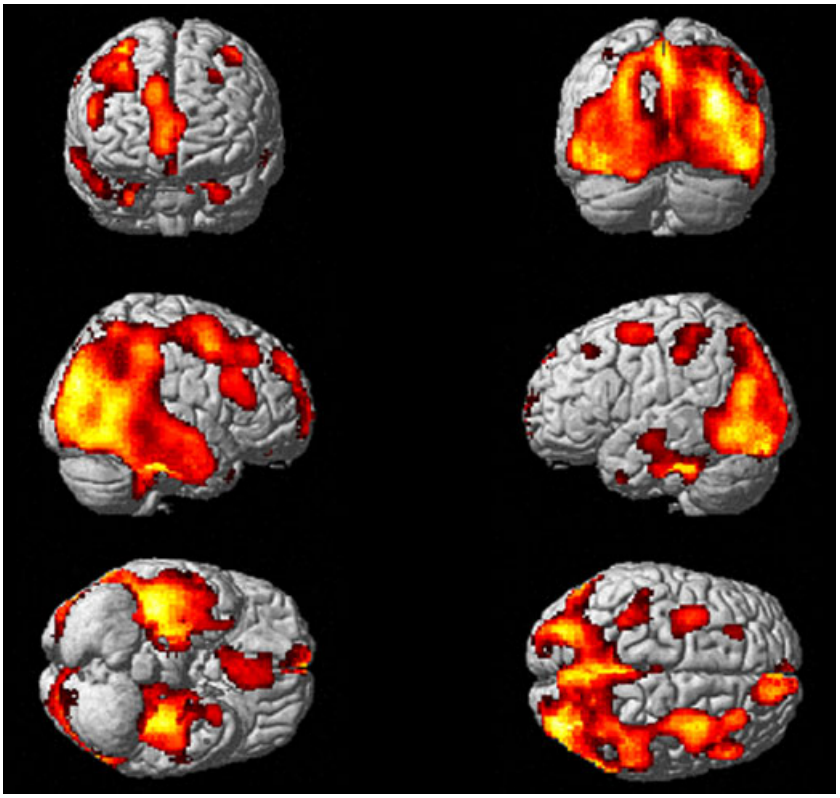

Figure 1 Significant deactivations [$P_{uncorrected} < 0.001$ (voxel level) and $P_{corrected} < 0.05$ (cluster level)] during gastric fundic distension at individually determined discomfort threshold (unpleasant/painful sensation) compared to baseline (C_1–C_4).

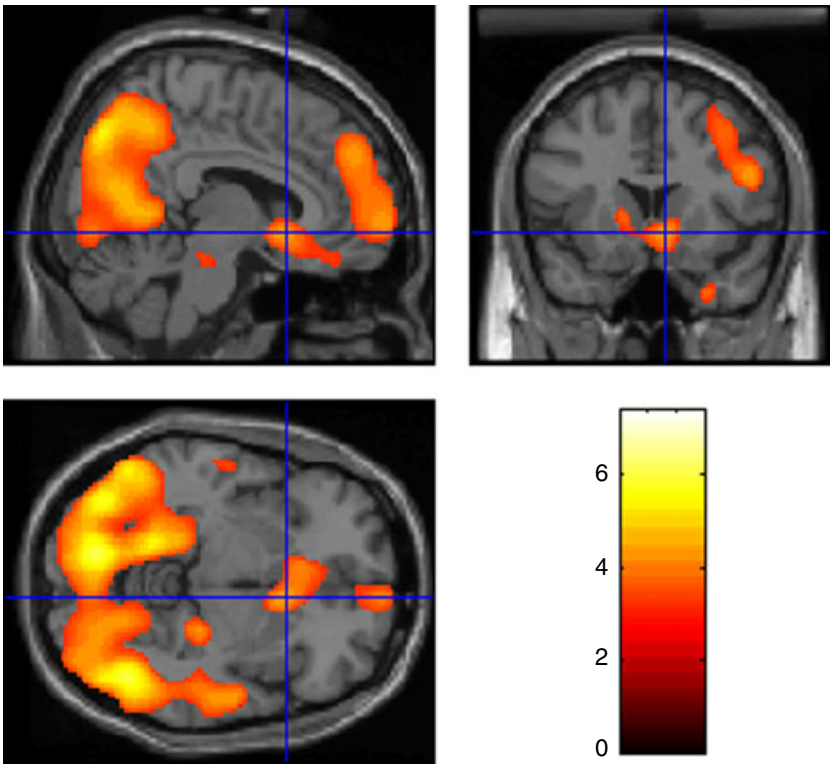

Figure 2 Significant deactivations during gastric fundic distension at individually determined discomfort threshold (unpleasant/painful sensation) compared to baseline (C_1–C_4) crosshairs at MNI coördinates (8,16,–6): right caudate head/subgenual ACC (cluster 3 in Table 1).

Table 2 Deactivations during gastric fundic distension at individually determined threshold for marked sensation compared to baseline (C_1–C_3)

MNI-coord local max x,y,z(mm)	Tentative anatomical localization	*t*-value (voxel level)	$P_{FDR\text{-corrected}}$ (voxel level)	$P_{FWE\text{-corrected}}$ (voxel level)	No. voxels	$P_{corrected}$ (cluster level)
2,–50,50	Right precuneus (BA 5/7)	5.74	<0.001	<0.001	21 843	<0.001
30,–82,28	Right middle occipital gyrus (BA 19)	5.65	<0.001	0.001		
36,–30,–32	Right cerebellum (VI)/fusiform gyrus (BA 37)	5.55	<0.001	0.001		
32,–18,54	Right precentral gyrus (BA 6/4a)	5.04	0.001	0.008		
26,–34,–16	Right fusiform/parahippocampal gyrus (BA 37/30)	4.95	0.001	0.011		
–24,–12,–26	Left hippocampus, includes amygdala	4.94	0.001	0.012		
–14,–86,–6	Left lingual gyrus (BA 17/18)	4.80	0.001	0.025		
50,–66,–10	Right inferior temporal/occipital gyrus (BA 37/19)	4.74	0.001	0.035		
–38,–66,–8	Left inferior occipital gyrus (BA 37/19)	4.65	0.001	0.045		
–42,–70,14	Left middle temporal/occipital gyrus (BA 37)	4.57	0.001	0.049		
–18,–56,–4	Left lingual gyrus (BA 19)	4.55	0.001	0.051		
4,–68,12	Right calcarine gyrus (BA 17/18)	4.54	0.001	0.104		
30,2,62	Right superior/middle frontal gyrus (BA 6/8)	4.16	0.002	0.169		
46,4,52	Right precentral/middle frontal gyrus (BA 6)	4.10	0.002	0.198		
–20,–30,–14	Left hippocampus, includes amygdala	4.03	0.002	0.239		
–24,–94,14	Left middle occipital gyrus (BA 18)	4.00	0.002	0.259		
24,–14,–24	Right hippocampus, includes amygdala	3.96	0.003	0.292		
–36,–42,–24	Left fusiform gyrus (BA 37)	3.88	0.003	0.357		
52,–44,20	Right superior/middle temporal gyrus (BA 41/42)	3.84	0.003	0.385		
40,–86,0	Right middle occipital gyrus (BA 19)	3.82	0.003	0.404		
2,–76,36	Midline (pre)cuneus (BA 7/18)	3.79	0.003	0.438		
–18,–34,4	Left hippocampus/ parahippocampal gyrus	3.28	0.009	0.565		
10,64,14	Left medial frontal gyrus (BA 10, vmPFC)	3.88	0.003	0.354	702	0.039

Significance threshold was set at $P_{uncorrected} < 0.001$ (voxel level); only clusters reaching significance at $P_{corrected} < 0.05$ (cluster level) were included in the table. Within each cluster, only local maxima more than 1 cm apart are shown.
BA, Brodmann Area; (dl/dm/vm)PFC, (dorsolateral/dorsomedial/ventromedial) prefrontal cortex; PCC, posterior cingulate cortex.

$t = 3.62$, $k = 153$, BA 20), left inferior frontal gyrus, pars triangularis (MNI-coordinates –42,34,14, $t = 3.45$, $k = 79$, BA 45), right angular gyrus (MNI-coordinates 38,–60,52, $t = 3.60$, $k = 71$, BA 39/7), left angular gyrus (MNI-coordinates –38,–62,44, $t = 3.31$, $k = 29$, BA 39) and left inferior parietal lobule (MNI-coordinates –46,–32,40, $t = 3.40$, $k = 47$, BA 40). None of these clusters reached significance at the cluster level of $P_{FWE\text{-corrected}} < 0.05$.

DISCUSSION

In summary, during gastric fundus distension in healthy humans, besides the activations reported earlier,[3] we found progressive cortical deactivations in occipital, posterior temporal and parietal (medial: precuneus and PCC; lateral: superior and inferior parietal lobule) areas, as well as in the hippocampus, amygdala, post- (SI) and precentral gyrus. Right dlPFC,

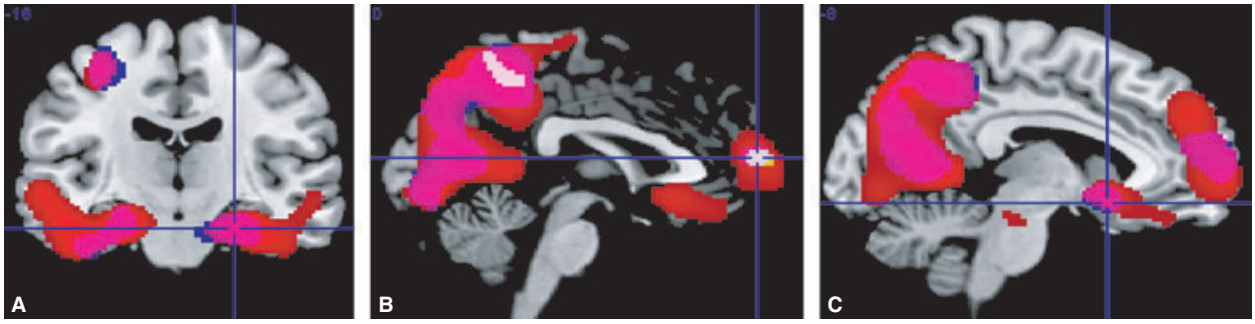

Figure 3 Areas commonly deactivated [($P_{uncorrected}$ < 0.001 (voxel level)] during unpleasant/painful sensation (C_1–C_4 in red), marked sensation (C_1–C_3 in blue) and weak/first sensation (C_1–C_2 in green), compared to baseline. (A) coronal section through the hippocampus/amygdala (y = −16). (B) midline sagittal section through the medial prefrontal and subgenual anterior cingulate cortex. (C) sagittal section through the left medial prefrontal and subgenual anterior cingulate cortex (x = −8).

Table 3 Deactivations during gastric fundic distension at individually determined discomfort threshold (unpleasant/painful sensation) compared to weak/first sensation threshold (C_2–C_4)

MNI-coord local max x,y,z(mm)	Tentative anatomical localization	*t*-value (voxel level)	$P_{FDR\text{-}corrected}$ (voxel level)	$P_{FWE\text{-}corrected}$ (voxel level)	No. voxels	$P_{corrected}$ (cluster level)
−26,−78,36	Left middle occipital gyrus (BA 19)	4.56	0.007	0.046	12 965	<0.001
30,−82,24	Right middle occipital gyrus (BA 19)	4.52	0.007	0.054		
18,−90,12	Right cuneus/calcarine gyrus (BA 18/19)	4.45	0.007	0.068		
26,−78,38	Right superior occipital gyrus (BA 19)	4.40	0.007	0.081		
−10,−72,54	Left precuneus (BA 7)	4.29	0.007	0.113		
4,-82,-4	Right lingual gyrus (BA 17)	4.23	0.007	0.137		
−14,−72,2	Left lingual gyrus (BA 17/18)	4.19	0.007	0.152		
10,−78,38	Right (pre)cuneus (BA 7/19)	4.12	0.007	0.187		
4,−82,30	Right cuneus (BA 18)	4.11	0.007	0.192		
18,−64,−4	Right lingual gyrus (BA 18/19)	4.06	0.007	0.225		
−36,−38,40	Left inferior parietal lobule (BA 40)	3.91	0.007	0.328		
−42,−36,54	Left postcentral gyrus (BA 2/3b)	3.89	0.007	0.346		
−16,−56,48	Left precuneus/superior parietal lobule (BA 5/7)	3.70	0.007	0.517		
−32,−58,42	Left inferior parietal lobule (BA 7)	3.59	0.008	0.627		
−40,−80,−4	Left inferior occipital gyrus (BA 19)	3.47	0.009	0.752		
18,−58,34	Right precuneus (BA 7)	3.33	0.011	0.774		
42,−42,−20	Right fusiform gyrus (BA 37/20)	5.23	0.007	0.004	1498	0.002
24,−20,−24	Right hippocampus	3.80	0.007	0.429		
58,−14,−6	Right superior temporal gyrus (BA 22)	3.74	0.007	0.480		
−32,−14,−26	Left hippocampus; includes amygdala, fusiform gyrus and inferior temporal gyrus	4.44	0.007	0.069	853	0.022
−46,−48,−2	Left inferior/middle temporal gyrus (BA 37)	4.18	0.007	0.159	790	0.028

Significance threshold was set at $P_{uncorrected}$ < 0.001 (voxel level); only clusters reaching significance at $P_{corrected}$ < 0.05 (cluster level) were included in the table. Within each cluster, only local maxima more than 1 cm apart are shown.
BA, Brodmann area; (dl/dm/vm)PFC, (dorsolateral/dorsomedial/ventromedial) prefrontal cortex; PCC, posterior cingulate cortex.

dmPFC and vmPFC were also deactivated, as well as sACC and caudate head. This pattern of deactivations was also found when intragastric pressure or gastric sensation score were correlated with brain activity (negative correlations). Deactivations in the right amygdala/hippocampus were specific to anticipation/sham.

Deactivations were defined in the present study as a reduction in regional cerebral blood flow during a certain 'active' condition compared to resting state ('baseline'). It should be noted, that their interpretation (unaccounted activations in resting state or 'true' deactivations during 'active' conditions; relationship with excitatory or inhibitory transmission processes) remains a matter of discussion in the literature, contrary to activations.[36] However, the present findings can, to our opinion, be interpreted in two ways, each of which will be discussed in detail below.

First, the deactivation pattern may be specific to (visceral) pain/interoception.

Cortical deactivations during gastrointestinal distension (oesophageal,[9] distal gastric[5] and rectal[13]), have been described before. Aziz *et al.* found deactivations during oesophageal distension in occipital areas, medial parietal cortex and left SI, right dlPFC and vmPFC.[9] Occipital and somatosensory deactivations were explained as attentional processes, 'filtering out other sensory processing'.[9] Medial prefrontal deactivation was interpreted as an antinociceptive response, a cognitive-affective evaluation of the painful sensation or the neural substrate of a coping strategy (inhibiting natural behavioural responses) towards a predictable, unavoidable pain stimulus.[9] Mayer *et al.* found deactivations in left 'rostral ACC' and bilateral dmPFC during rectal distension in healthy controls but not in IBS patients.[13] As these regions are involved in anticipatory, attentionally or affectively driven pronociceptive pathways [through inhibitory projections to the periaqueductal gray (PAG)],[44–49] this was interpreted by the authors as an adaptive antinociceptive response, which is defective in IBS.[13] Song *et al.* found deactivations during actual and sham rectal distension as well as heterotopic stimulation (rectal distension plus foot cold pressor test) in (subgenual) ACC, PCC and hippocampus in both healthy controls and IBS patients. Deactivations have also been reported during somatic pain.[50,51] Vogt *et al.* found deactivations in vmPFC/sACC, PCC and parietal cortex,[20] explained as 'a result of inhibition of visually guided movements'. Hsieh *et al.* described deactivations during cutaneous pain,[17] the location of which was comparable to our present findings: bilateral dlPFC, posterior temporal cortex, inferior and posterior lateral parietal cortex, right occipital cortex and right hippocampus. The authors interpret this as 'functionally inhibitory control for attention to pain over cortical areas dedicated to other cognitive dimensions'.[17] Most of the explanations described in this paragraph may equally apply to our present results, as will be discussed below.

In the present study, deactivations were found in occipital, posterior temporal and parietal areas. The majority of these areas are uni- or heteromodal sensory regions[52,53] that are mainly involved in processing exteroceptive information (tactile, visual, auditory). Taken together with the activations in interoceptive-sensory regions (SI/SII, insula),[3] their deactivation may be explained as the neural correlate of a shift from mainly exteroceptive (during baseline) to interoceptive processing (during gastric distension). Gregory *et al.* have shown that divided attention to visual and oesophageal stimuli recruits visceral sensory (insula, SI/SII) and cognitive (ACC, PFC) cortical areas rather than visual cortical areas. This 'may reflect a processing prioritization for sensations arising from the viscera, even when there is competition for neural resources from other sensory modalities, because sensations arising from the viscera are often important indicators of tissue damage, inflammation, or potential harm to an organism'.[54] Dunckley *et al.* recently found that increasing pain intensity was associated with decreasing neural activity in the primary and secondary auditory cortex as well as the temporoparietal junction, independent of the direction of attention (towards auditory or pain stimulus).[55] This is consistent with a mechanism by which attention (and its neural resources) is shifted from exteroception towards interoception during (visceral) pain processing.

The medial temporal lobe (hippocampus/amygdala) is another area that is bilaterally deactivated in the present study. The hippocampus, besides its well-known function in explicit memory, also integrates sensory, cognitive and emotional information; it may therefore play a role in emotional regulation.[52,53,56,57] The exact role of the hippocampal deactivations remains a matter of speculation. Given these functions of the hippocampus, we may speculate that its deactivation represents cognitive/affective processes, whether or not directly related to visceral stimuli (for example, explicit memories related to previous experience of noxious interoceptive stimuli). The amygdala is involved in emotional responses, especially fear, but is also receiving viscerosensory input.[53,58,59] Amygdala deactivation has been reported in somatic pain;[23,27,60] this may represent an adaptive pain modulatory response to an unavoidable noxious stimulus, attenuating the stress-response generated by the stimulus.

There is also evidence that this response is controlled by 'higher' (cognitive) cortical areas (vlPFC, pACC),[27] regions activated during gastric distension.[3] In the present study, the right amygdala/hippocampus deactivation was also observed during sham, suggesting that this adaptive pain modulatory response is driven by anticipation. Thus, in healthy volunteers, the response takes place not only during actual visceral distension, but also during its anticipation. This mechanism may be deficient in patients, although this remains to be elucidated. However, the only study reporting changes in amygdala activity during gastric distension found the amygdala to be activated during distension,[4] which was also the case in some studies on rectal sensation.[13]

Deactivations were also found in prefrontal areas. First, deactivations were found in right dlPFC. The dlPFC is involved in 'executive functions', including directing/shifting attention towards relevant sensory information, organizing and integrating this information and keeping it in mind ('working memory') and developing response strategies.[52,53] The dlPFC interacts with other parts of the PFC (OFC, ACC) to integrate exteroceptive information with information about the internal milieu and emotional valence.[52,53] We may speculate that the deactivation in dlPFC is the neural substrate of a cognitive (attentional, response selection?) response to noxious visceral distension in health. Second, deactivations were found in right dmPFC. The dmPFC has been reported to be deactivated during actual and anticipated noxious rectal distension in controls but not in IBS patients.[13] The dmPFC is important in endogenous antinociception, through inhibitory connections with the PAG.[13,61] The right vlPFC, or lateral (l)OFC is positively connected to the PAG, probably through an inhibitory connection with the dmPFC.[13,49] The right vlPFC activation[3] and right dmPFC deactivation are therefore consistent with an adaptive antinociceptive response in healthy volunteers. Finally, the right vmPFC was also found to be deactivated. The vmPFC, or medial (m)OFC, is connected to limbic structures and provides the major cortical output to visceromotor structures in the hypothalamus and the brainstem.[62,63] The vmPFC is connected to the adjacent vlPFC/lOFC, which is receiving input from visceral afferents and other sensory modalities, especially related to food and eating, as well as from limbic emotional regulation areas.[62,63] Thus, the vlPFC/lOFC can be seen as a viseral sensory – emotional integration area, whereas the mOFC serves as a visceromotor response system. Both systems interact closely and are critically involved in mood (dys)regulation.[62,63] The orbitofrontal cortex plays a central role in linking food and other reinforcers or punishers to reward and affective value as well as hedonic experience.[64] A recent meta-analysis links mOFC activation to the monitoring, learning and memory of the reward value of reinforcers, whereas lOFC activity is related to the evaluation of punishers.[64] The deactivation in the mOFC in the present study, together with the previously published activation in the vlPFC/lOFC,[3] is consistent with processing of a negative internal event or 'punisher', according to the medial-lateral distinction outlined above. The sACC is sometimes considered to be a (functional) part of the vmPFC/mOFC.[64,65] It is involved in emotional regulation and autonomic, visceromotor and anti-nociceptive responses (through connections with the amygdala, PAG and brainstem nuclei).[57,65] This deactivation may thus be interpreted as an affective, autonomic, visceromotor and/or antinociceptive response, although this remains a matter of speculation. As the striatum (caudate and putamen) is part of several parallel fronto-subcortical circuits,[53,66] the deactivation in the caudate head may be part of an (inhibitory) motor (motor cortex circuit), cognitive (dlPFC circuit), or affective-motivational (orbitofrontal and ACC circuit) response.

Second, the overall pattern of deactivations found in the present study is consistent with attenuation of 'default mode' brain function during gastric distension compared to 'rest' or 'baseline',[28,30,31] as it is remarkably similar to a large body of evidence on task-deactivations when various cognitive-perceptual tasks are compared to 'baseline' (i.e. lying quietly with eyes open).[30,32–34] These deactivations are located mainly in lateral and medial (precuneus and adjacent PCC) parietal cortex, medial prefrontal areas and adjacent ACC and medial temporal lobe [amygdala, (para)hippocampus] and are strikingly task-independent. It is suggested that tonic activity in these areas during 'rest' or 'baseline' may represent gathering and evaluation of general information from various sources in the external and internal milieu. When focused attention is required (for example when novel extero- or interoceptive stimuli are presented), the tonic activity involved in general information processing is attenuated in favour of specific processing of the relevant stimulus.[28,30] Thus, the deactivations in the present study may be largely stimulus- or task-independent. However, to the best of our knowledge, no previous study examined the effect of gastrointestinal stimuli on 'default network' activity. It should be noted that this interpretation may be complementary to, rather than at variance with some of the (visceral) pain-specific interpretation given above,

especially the shift from exteroceptive to interoceptive processing.

Some limitations of the present study need to be addressed. First, although the deactivations found in the present study are generally in line with previous findings on gastrointestinal distension, as discussed above, some of the discrepancies found may be due to gender differences. Unlike in some other studies, the gender ratio was more or less equal in the present study and gender has been shown to influence regional brain activation during gastrointestinal distension.[67] Second, the limited resolution (which is a combination of the intrinsic resolution of the system and the width of the smoothing kernel) may decrease the sensitivity for detecting activations in smaller areas (e.g. in subcortical nuclei) and may decrease the ability for the exact anatomical localization. Re-analysis with a smaller kernel width, however, did not result in detection of different areas.

CONCLUSION

This is the first article reporting on cortical deactivations during noxious gastrointestinal distension in detail. In the healthy volunteers from our previously published study,[3] we found a pattern of progressive deactivations, besides the activations reported earlier,[3] in occipital, parietal, posterior temporal and prefrontal (dm/vmPFC, sACC) cortex, and in medial temporal (hippocampus/amygdala) regions.

Whether these deactivations mainly represent a stimulus-independent attenuation of 'default mode' of brain function (processes underlying general information gathering and evaluation) or visceral pain/interoception-specific processes (including affective, cognitive and pain modulatory responses) remains to be elucidated.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article.

Table S1. Regions in which activity correlates negatively with intragastric pressure

Table S2. Regions in which activity correlates negatively with gastric sensation score

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