CORTICAL PROCESSING OF VISCERAL AND SOMATIC STIMULATION: DIFFERENTIATING PAIN INTENSITY FROM UNPLEASANTNESS

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Abstract—Visceral and somatic pain perception differs in several aspects: poor localization of visceral pain and the ability of visceral pain to be referred to somatic structures. The perception of pain intensity and affect in visceral and somatic pain syndromes is often different, with visceral pain reported as more unpleasant. To determine whether these behavioral differences are due to differences in the central processing of visceral and somatic pain, non-invasive imaging tools are required to examine the neural correlates of visceral and somatic events when the behavior has been isolated and matched for either unpleasantness or pain intensity. In this study we matched the unpleasantness of somatic and visceral sensations and imaged the neural representation of this perception using functional magnetic resonance imaging in 10 healthy right-handed subjects. Each subject received noxious thermal stimuli to the left foot and midline lower back and balloon distension of the rectum while being scanned. Stimuli were matched to the same unpleasantness rating, producing mild-moderate pain intensity for somatic stimuli but an intensity below the pain threshold for the visceral stimuli. Visceral stimuli induced deactivation of the perigenual cingulate bilaterally with a relatively greater activation of the right anterior insula-i.e. regions encoding affect. Somatic pain induced left dorso-lateral pre-frontal cortex and bilateral inferior parietal cortex activation i.e. regions encoding spatial orientation and assessing perceptual valence of the stimulus. We believe that the observed patterns of activation represent the differences in cortical process of interoceptive (visceral) and exteroceptive (somatic) stimuli when

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E-mail address: irene.tracey@human-anatomy.oxford.ac.uk (I. Tracey). Abbreviations: BA, Brodmann's area; BOLD, blood oxygen level dependant; DLPFC, dorso-lateral pre-frontal cortex FILM, Functional Magnetic Resonance Imaging of the Brain's improved linear model; FMRI, functional magnetic resonance imaging; FMRIB, Functional Magnetic Resonance Imaging of the Brain; pACC, perigenual cingulate; PE, parameter estimate; ROI, region of interest; SI, primary somatosensory cortex; SI, secondary somatosensory cortex; TE, echo time; TR, repeat time; VMPFC, ventromedial prefrontal cortex.

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Visceral and somatic pain have several key perceptual differences. Visceral pain is poorly localized and is often referred to somatic regions. These properties are likely to be secondary to differing peripheral neuronal characteristics—viscero-somatic convergence and divergence of visceral afferents. Other perceptual differences must be centrally driven. For example, sensation from the internal viscera is likely to recruit cortical regions involved in interoception (sensation of the physiological self) (Craig, 2002), somatic sensation is more likely to induce activation in cortical regions responsible for exteroception and spatial orientation. Furthermore, noxious stimulation tends to induce divergent behavioral patterns: visceral pain results in quiescence whereas somatic pain results in a flight and fight response (Lumb, 2002).

Visceral sensation is commonly described as more unpleasant than somatic sensation (Strigo et al., 2002; Verne et al., 2001). In a psychophysical study comparing visceral and somatic sensation, Strigo et al. (2002) discovered that while healthy subjects rated the unpleasantness and intensity of thermal stimulation to the anterior chest wall similarly, they rated the unpleasantness of esophageal distension proportionately greater than the intensity. This divergence of the affective quality of the visceral and somatic pain experience allows for the investigation of the differences in cortical representations between the two sensory modalities.

Numerous imaging studies have led to a better understanding of the cortical networks responsible for the processing of somatic pain. Visceral imaging studies are sparse in comparison (Aziz et al., 2000; Mertz et al., 2000; Hobday et al., 2001; Lotze et al., 2001; Naliboff et al., 2001; Kern et al., 2001; Verne et al., 2003). While areas similar to those activated during somatic experiments are commonly seen, there are also differences in cortical activation patterns between visceral and somatic stimuli. Investigators have examined the cortical representations of visceral (rectal) and somatic (anal) sensation arising from the gastrointestinal tract (Hobday et al., 2001; Lotze et al., 2001) and found similar areas of cortical activation with greater motor cortex involvement for the anal canal.

Support for common pain processing regions for the two sensory modalities also comes from a human study of lower esophageal distension and cutaneous heat in the same subjects administered at levels where pain intensity and unpleasantness were similar between the two modalities (Strigo et al., 2003). In this study, while the authors matched intensity and unpleasantness for the two sensory modalities, the ratings for unpleasantness were generally higher than those for intensity for noxious esophageal stimulation but were similar after cutaneous stimulation. Although similar brain regions were activated, greater activation was observed in the anterior insula bilaterally and the left ventrolateral prefrontal cortex in the somatic group. There were also differences in the activation of the somatosensory and anterior cingulate cortices between visceral and somatic stimuli. Greater activation was demonstrated in a relatively more rostral subregion of the midcingulate cortex for esophageal distension and a more dorsal subregion for cutaneous stimulation. Therefore, although similar brain areas are activated by somatic and visceral pain, differences also exist. These differences may be due to differential patterns of cerebral activation to visceral and somatic stimuli or alternatively could be due to the greater unpleasantness associated with visceral stimuli (Strigo et al., 2003). The precise reasons for the differences observed remains unclear.

What has not been performed is a study where unpleasantness to a visceral and somatic stimulus has been matched, with concomitant differences in the pain intensity needed to produce a matched unpleasantness (i.e. if visceral stimulation is more unpleasant that somatic stimulation, a lower pain intensity is needed for visceral stimulation compared with somatic to drive the same unpleasantness rating). This would allow selective investigation of the differences between the two sensory modalities in the brain regions responsible for intensity and affective coding.

The aim of this study was therefore to identify the differences in cortical activation of visceral and somatic noxious stimulation specifically matched for unpleasantness.

EXPERIMENTAL PROCEDURES

Subjects

Ten healthy right-handed subjects (five female, median age 30 years, range 22–32) were recruited to participate in the study. None reported any abnormal gastrointestinal or somatic symptoms on personal history and bowel symptom questionnaire (Talley et al., 1989). Clinical depression was excluded with the use of the Beck's Depression Inventory (Beck et al., 1961). None of the subjects were taking any regular medication likely to interfere with the functional magnetic resonance imaging (FMRI) results. All subjects gave informed consent and the Oxfordshire Clinical Research Ethics Committee approved the study.

Somatic stimulation

Thermal stimuli were delivered via a magnet-compatible 1 cm×2 cm thermal resistor (Centre for the Functional Magnetic Resonance Imaging of the Brain (FMRIB), Oxford, UK). The device has a rapid ramp time of 30–60 °C in 0.8 s. On separate scanning sessions, the thermal resistor was attached to the dorsum of the left foot (L5) or the midline of the lower back (L5).

Visceral stimulation

Rectal stimulation was delivered using a 2 cm long latex balloon. This was attached to a 50 cm long polyvinyl catheter (3 mm internal diameter) and connected via an 8-m length of polyvinyl tubing (4 mm internal diameter) to a purpose-designed mechanical pump (Medical Physics Department, Hope Hospital, Manchester, UK), which was placed outside the magnet room. The time to maximal inflation ranged from 140 to 160 ms. The balloon was inserted into the rectum, 10 cm from the anal verge.

Experimental design

Each subject had three separate scanning sessions; for two somatic regions (dorsum of left foot and mid-line lower back both at the level of L5) and one visceral region (rectal). Lateral and mid-line somatic stimuli were chosen because little is known of hemispheric dominance of visceral pain processing or of midline somatic structures. The order of scans was randomized for each subject. Once the thermal resistor had been attached or balloon inserted the subject was moved into the scanner and made comfortable. Foam padding was placed around the subject's head to minimize head movement. Earplugs were used along with electrostatic headphones (MRC Institute of Hearing Research, Nottingham, UK). Prior to the scanning run, a series of increasing thermal/mechanical balloon stimuli, each lasting 3 s, was then delivered. The subjects were required to rate each of these stimuli for intensity, unpleasantness and urge (balloon distension) (Kwan et al., 2002). Numerical rating scales ranging from 0 to 10 were used for each sensation. The range of intensity ratings was defined as 0 (no sensation), 1 (stimulus just perceptible, i.e. sensory threshold), 5 (pain begins, i.e. pain threshold) and 10 (intense pain). This allowed the rating of a larger range of intensities. This was necessary as some subjects did not rate the balloon distension as painful even at the higher volumes. The descriptors used for the unpleasantness numerical rating scale were "not unpleasant" (0) and "excruciating" (10). Urge sensation was scored from 0 (no urge) to 10 (intense urge). Each subject was trained to use these scales prior to entering the magnet. The aim of this initial testing was to identify the temperature or pressure required to induce a reliable unpleasantness rating of 4 of 10. This was then used for the remainder of the experiment.

An event-related paradigm was used. Each subject received 20 3 s stimuli with an average 60 s inter-stimulus interval. The stimulus onset was "jittered" randomly to MR data acquisition thereby enabling correct sampling of the hemodynamic response function across brain regions. Ten seconds after each stimulus the numerical rating scale was projected via an Infocus FP1000 projector (Infocus, Wilsonville, OR, USA) onto a screen visible to the subject via prism glasses. The subject was then able to move an arrow on the scale to indicate the rating for the prior stimulus with the use of a magnet-compatible button box (Centre for the Functional Magnetic Resonance Imaging of the Brain).

FMRI scanning protocol

Subjects were scanned in a 3 Tesla human MRI system (Oxford Magnet Technology) with the use of a Magnex SGRAD MK III head insert gradient coil (Magnex Scientific Ltd, Oxford, UK). A birdcage radio-frequency coil was used for pulse transmission and signal reception. For each subject, whole-brain T2*-weighted echo-planar imaging was utilized for the functional scans, which consisted of 24 contiguous, 6 mm, axial slices. The following parameters were used: repeat time (TR) 3000 ms, echo time (TE) 30 ms, flip angle 90°, field of view 256×192 mm, and a matrix size of 64×64 . A high-resolution, T1-weighted, 3D Turbo FLASH scan (64 contiguous 3 mm axial slices, TR 15 ms, TE 5 ms, field of view 256×192 mm, and matrix 256 $\times 192$ mm, and analysis.

Image analysis

Image analysis, aimed at delineating significant brain activation via changes in the blood oxygen level dependent (BOLD) signal (Ogawa et al., 1992), was performed on each subject's functional data set with the use of FEAT (FMRIB Expert Analysis Tool) (www.fmrib.ox.ac.uk) (Smith et al., 2001). Prior to the statistical analysis the data were motion corrected with the use of Motion Correction using FMRIB's Linear Image Registration Tool (MCF-LIRT) (Jenkinson et al., 2002), spatial smoothing was carried out with a Gaussian kernel of full-width-half-maximum 5 mm, intensity normalization was performed with a single scaling factor and high-pass temporal filtering performed with a Gaussian-weighted least squares straight line fit and high-pass cutoff filter of 60 s. The statistical analysis was performed with FMRIB's improved linear model (FILM) (Woolrich et al., 2001). A model of the relevant applied stimuli and confounds was thus designed and convolved to the hemodynamic response function. This convolved model was then fitted to the four-dimensional data set to demonstrate areas of brain activation. FILM uses a robust and accurate nonparametric estimation of time series autocorrelation to prewhiten each voxel's time series; this gives improved estimation efficiency compared with methods that do not pre-whiten.

An event-related paradigm was used. The stimulus timings were designed into the model as the stimulus explanatory variable. Further explanatory variables were designed for the numerical rating scales, which were then modeled out at the final analysis. Each voxel was then analyzed against the convolved model with a resultant parameter estimate (PE) image. The PE is an estimate of how well each voxel fits the convolved model: the higher the PE, the better and greater the fit. Cluster thresholding with significance estimation defined by Gaussian Random Field Theory was used to identify clusters of significantly activated voxels (*z*-score>2.3, P<0.01). The functional data set was coregistered onto the subject's high-resolution T1-weighted scan, which was then registered onto a standard brain (Montreal Neurological Institute 152 brain).

A mixed effects (often referred to as a "random effects") group analysis was performed for each of the three groups with FMRIB's Local Analysis of Mixed Effects (FLAME). This incorporates variance within session and across time (fixed effects) and cross session variances (random effects). Cluster thresholding was performed with a *z*-threshold of 2.3 and corrected *P*-value of <0.01 (Worsley et al., 1992; Friston et al., 1994).

Left and right-sided region of interest (ROI) masks were then defined for the key areas: the thalamus, insula cortex (anterior and posterior), cingulate cortex (mid and perigenual), and secondary somatosensory cortex (SII). The mean PE was then calculated for each ROI for each subject's data set. Significant differences between the somatic and visceral mean group PE for each ROI were tested with a two-tailed Student's *t*-test.

RESULTS

Psychophysical

All subjects tolerated the study well. The mean ratings for intensity, unpleasantness and urge are shown in Fig. 1. There were no significant differences in unpleasantness ratings between groups (P>0.05, two-tailed paired Student's *t*-test). Intensity ratings were significantly higher for somatic stimulation compared with rectal stimulation (P<0.001, two-tailed paired *t*-test). Rectal balloon distension induced a mean urge score of 3.99 (S.E.M.=0.46). Most subjects reported that the unpleasant nature of the balloon distension related to the urge to defaecate that they felt. The mean temperatures used were 52.59 °C



Fig. 1. Psychophysical data. The unpleasantness ratings were matched with no significant differences between the three groups (NS=non-significant, paired Student's *t*-test). Significantly greater intensity ratings were found for mid-line back and left foot stimulation in comparison to rectal stimulation (* P<0.01, paired Student's *t*-test). Standard error bars are shown.

(S.D. 3.86) for the mid-line back, and 53.59 °C (S.D. 2.98) for the left foot. The mean pressure for rectal balloon distension was 24.36 psi (S.D. 15.42).

Brain activation

Marked similarities in the location of activated cortical regions were observed for each group, with the typical "pain matrix" pattern of activation present [Figs. 2 and 3]. Bilateral activation was seen in each of the group analyses in the thalamus, insular cortex along its anterior-posterior axis, the mid-cingulate cortex, brainstem, supplementary motor area, and globus pallidus. A region incorporating the lateral, inferior primary motor cortex extending anteriorly to the pre-motor region and Brodmann's area (BA) 44 was activated in all three groups. Bilateral activation of the SII cortex was also demonstrated for left foot and midline back stimulation, but only right-sided activation of SII was observed during visceral stimulation. Bilateral and right-sided posterior parietal cortex (Brodmann's area 40) activation was present for mid-line back and left foot respectively, but was absent for rectal stimulation. Left dorso-lateral prefrontal cortex (DLPFC) activation was present solely in the back group. Peak z-statistic co-ordinates for each region and each stimulus type are shown in Table 1.

ROI analysis

Further analysis of the data revealed sub-threshold activation of the left SII cortex in the rectal group (peak z-scores are shown in Table 1). Thus, despite not reaching the z threshold of 2.3, significant differences were not seen between rectal and somatic data sets for these regions (data not shown), despite the apparent absence of activation in Fig. 2. The only regions to show significant differences on ROI analysis were the left and right perigenual cingulate (pACC) (Fig. 4). Rectal stimulation resulted in a reduction in left and right pACC activity that was statistically significantly lower than both foot and back stimulation (Student's paired *t*-test P<0.05, two tailed). Group subtraction analysis confirmed this difference: subtraction of the somatic



Fig. 2. Group activation maps for (a) mid-line back, (b) left foot and (c) rectal stimulation. Axial slices are shown through the brainstem (BS), thalamus (THAL) and insula (INS) cortex and inferior parietal cortex (IPC), along with a sagittal slice through the mid-cingulate cortex (mid-ACC) and coronal slice through the SII (L, left; R, right). A similar bilateral network of activity is seen with all three stimulation types. SII activation is sub-threshold (*z*-score<2.3) for rectal balloon distension. Main differences are of bilateral inferior parietal cortex activity in the somatic groups only along with left dorsolateral prefrontal cortex in the mid-line back group only. GP, globus pallidus; PMC, pre-motor cortex; SMA, supplementary motor cortex.

groups from the visceral group resulted in a significant region of pACC deactivation (Fig. 5). Significant deactivations were also seen for the ventromedial prefrontal cortex (VMPFC) and posterior cingulate cortex in the visceral group compared with the two somatic groups. Furthermore, there was a significant negative correlation between left and right visceral pACC mean PE and mean urge score (Pearson's correlation, Left pACC r=-0.75, P<0.05, Right pACC r=-0.69, P<0.05, two-tailed) (Fig. 6).

Visceral pain is often reported as more unpleasant than somatic pain (Strigo et al., 2002, 2003). We therefore went on to investigate the relationship between pain perception of intensity and unpleasantness within two key areas of the pain matrix thought to be involved in processing the affective/cognitive/interoceptive components of pain perception (anterior cingulate and insula cortices). This was done to better determine how pain intensity drives or relates to pain unpleasantness perception. We



Fig. 3. Binary overlap map: the activation map for each group binarized and overlapped in standard (MNI) space. Blue represents activation in one group only; red, overlap between two groups and yellow, three groups. L, left; R, right.

Table 1	. Co-ordinates	for the pe	ak z-scores	within the	activated	brain regions
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	Side	Midline back		Left foot		Rectum	
Cortical region		Co-ordinates	z-Score	Co-ordinates	z-Score	Co-ordinates	z-Score
Insular cortex	Right anterior	36, 20, -6	5.13	42, 8, -12	4.71	38, 18, -4	4.3
	Left anterior	-36, 14, 0	4.77	-34, 16, 4	3.96	-38, 12, -4	5.15
	Right posterior	38, -20, 0	4.02	38, -14, -8	4.01	36, -20, 12	4.02
	Left Posterior	-40, -16, -8	3.88	-36, -18, 4	3.6	-38, -18, -2	3.51
Mid-cingulate	Right	2, 20, 22	3.4	10, -6, 40	3.48	8, 24, 28	3.94
cortex	Left	-4,22, 24	3.99	-8, 20, 26	4.07	-2, 14, 30	4.07
SII	Right	56, -26, 24	3.03	58, -24, 26	3.82	58, -26, 24	4.55
	Left	-52, -28, 18	3.42	-58, -22, 22	3.64	_	_
Thalamus	Right	6, -20, -2	3.63	6, -18, 0	3.29	10, -14, 0	3.58
	Left	-10, -18, 0	3.51	-4, -16, -2	3.2	-10, -12, -2	2.87
Globus	Right	14, 2, -2	4.04	12, 2, -2	3.37	20, 0, -8	4.25
pallidus	Left	-18, 0, -2	2.3	-12, 2, -2	3.24	-22, 2, -8	3.77
Brainstem	Right	8, -16, -10	3.62	2, -30, -8	3.71	4, -18, -16	3.51
	Left	-6, -20, -12	3.06	-10, -14, -8	3.6	-6, -18, -16	3.25
SMA	Right	4, 2, 48	4.04	4, 10, 52	3.65	2, 2, 50	4.48
	Left	-4, 2, 46	4.28	-8, 2, 60	3.39	-4, 2, 52	4.51
Inferior parietal	Right	60, -40, 32	3.52	50, -32, 42	2.9	_	_
cortex	Left	-44, -36, 44	3.06	-52, -38, 28	2.67	_	_
DLPFC	Left	-32, 40, 24	3.14	—	—	—	_

Co-ordinates are given in the space of Montreal Neurological Institute (152 average brain). DLPFC, dorsolateral prefrontal cortex; SII, secondary somatosensory cortex; SMA, supplementary motor cortex.

divided the mean PE for the right and left anterior and posterior insula (divided anatomically into an anterior and posterior division) by the pain intensity ratings for each group, and did the same for anterior cingulate cortex. This gave us a ratio of activation per intensity rating unit. Thus, given the relatively greater affective component of visceral pain processing (seen in this study as a reduction in the visceral intensity ratings when unpleasantness is matched), regions encoding visceral unpleasantness would be expected to have greater ratios than somatic. As we matched unpleasantness not intensity, yet obtained the same activation within a few key regions, we hypothesize that the encoding of visceral unpleasantness would be expected to have greater ratios therefore of brain activity-pain intensity perception within these regions compared with similarly derived somatic ratios. This could represent brain areas which preferentially encode visceral unpleasantness or interoception. In other words, as a smaller intensity drives a greater unpleasantness response in visceral sensation, a greater ratio of mean PE for a given ROI per intensity rating unit would be expected in regions encoding visceral unpleasantness or interoception when compared with somatic ratios. Fig. 7a shows the mean PE for the right and left mid-cingulate, posterior and anterior insula cortices. Fig. 7b shows the ratio values. We found the right anterior insula cortex is activated proportionally greater in the visceral group (per intensity unit) compared with either of the somatic groups. This difference in ratio was significantly greater for visceral compared with the other mid-line structure: the mid-line back (P < 0.05), but did not reach significance when comparing visceral and left foot processing (P=0.11). The other five regions showed no significant differences between visceral and somatic ratios.

DISCUSSION

These results confirm that, when matched for the affective dimension of pain (unpleasantness), noxious visceral and somatic stimulation activate a complex, mainly bilateral network of cortical structures. Similarities in the spatial localization of the regions activated are marked, particularly in the insular cortex, anterior cingulate cortex and right SII (Figs. 2, 3). ROI analysis has demonstrated a novel finding: bilateral pACC deactivation in the visceral group alone, whereas all other regions were similarly activated. Group subtraction analyses confirmed a significant deactivation of the pACC in the visceral group compared with the somatic groups. The VMPFC and posterior cingulate cortices also deactivated in the visceral group (Fig. 5). The relevance of the posterior cingulate deactivation in the visceral group warrants further investigation. Unlike previous studies, we have specifically controlled the unpleasantness of the visceral and somatic stimulation. This has allowed us to investigate the relative contributions of regions encoding visceral unpleasantness. Ratio data have highlighted a relatively greater level of right anterior insula cortex activity per intensity unit ratings during visceral stimulation (Fig. 7b).

Somatosensory cortices

ROI analysis has demonstrated no significant differences in the strength of activation in regions of interest except the pACC, despite the notable differences in the psychophysical data (i.e. lower intensity ratings for rectal stimulation com-



Fig. 4. Mean PE change for the (a) right pACC cortex and (b) left pACC cortex. A significant de-activation is seen in the rectal group with very little activity in the somatic groups (* P<0.05, two-tailed paired Student's *t*-test).

pared with somatic stimulation). This suggests an upregulation of visceral processing in any regions responsible for intensity coding such as the SII and posterior insula cortices, has occurred. Failure to activate primary somatosensory cortex (SI) in our experiment with either the visceral or somatic stimuli is likely to relate to the small thermode and relatively small balloon used. Inconsistent SI activation may reflect the relatively small region of activa-

tion, variable sulcal anatomy, adjacent inhibition/reduction in BOLD signal in SI neurones, and the need for spatial summation of noxious stimuli (Bushnell et al., 1999; Peyron et al., 2000). SII activation is commonly found in noxious somatic imaging studies and in approximately half of visceral imaging studies (Peyron et al., 2000; Derbyshire, 2003). Activation is almost always bilateral or contralateral to the side of stimulus. This is in agreement with the neuronal characteristics of this region, which exhibit large bilateral fields. Using thermal pain Coghill et al. (2001) demonstrated intensity coding characteristics of SII. Despite a significant difference in pain intensity ratings in this experiment, no significant difference in SII activation was seen between somatic and visceral stimulation. Thus it is possible that, even at non-painful levels, the visceral stimulation crossed an "all-or-nothing" threshold (Timmerman et al., 2001) resulting in SII activation approaching that seen in somatic stimulation.

PACC cortex

The only significant difference seen on ROI analysis was a deactivation of the pACC in the visceral group. Although controversy remains, reductions in BOLD response are likely to represent neuronal deactivations, thus representing stimulus-related reduction in neuronal activity. pACC activity reductions have been seen during anticipation to painful stimuli (Porro et al., 2003; Simpson et al., 2001) and have correlated with increased heart rate associated with pain anticipation (Porro et al., 2003). Furthermore, pACC de-activation is seen in cognitively demanding tasks such as the Stroop task (Bush et al., 2000). There are several possible explanations for the pACC de-activation found during rectal stimulation. It is possible that the deactivation in our study represents a heightened level of anticipation to a novel visceral stimulus or of arousal and attention needed to rate it, i.e. regions involved in cognitive processing actively suppress pACC activity. It is notable that all subjects reported increased difficulty in accurately rating the visceral sensation, as it is obviously a novel stimulus for most subjects. Alternatively, the diffuse, poorly



Fig. 5. Group subtraction analyses. (a) The back group subtracted from the visceral group and (b) the left foot group subtracted from the visceral group. Regions of significant deactivation (z<-2.3, P>0.01) are seen in the pACC cortex (peri-ACC) in both subtraction analyses. VMPFC and posterior cingulate cortex deactivations are also present.



Fig. 6. Correlation of mean urge rating during balloon distension with (a) mean right pACC PE and (b) mean left pACC PE. A significant negative correlation is present for each side and urge sensation (right: r=-0.75, n=10, P<0.05, two tailed; left: r=-0.69, n=10, P<0.05, two tailed).

localized nature of visceral sensation made the rating more difficult and thus required a greater attentive effort. Other studies of visceral pain have reported increased pACC activity during balloon inflation (Silverman et al., 1997; Kern et al., 1998; Naliboff et al., 2001). None of these studies required the subjects to provide an online (i.e. in the scanner) behavioral feedback as was used in our study. It is feasible therefore that there was a lack of cognitively driven pACC inhibition with consequential activation through the dominant emotive perceptions associated with visceral pain induced by balloon distension. Visceral sensation/pain induces a passive emotional coping strategy with quiescence and vasodepression as opposed to the flight/fight response of cutaneous pain (Lumb, 2002). These responses are felt to be in part encoded by the peri-aqueductal grey which is in turn closely linked with the pACC. Lesions of the pACC produce similar behavioral quiescence and vasodepression responses (Phillips et al., 2003b). Thus an alternative explanation for reductions in activity in the pACC may be the neural response of a passive emotional response. The correlation with urge sensation would support this theory. However, other studies of visceral pain have reported pACC activation (Silverman et al., 1997; Kern et al., 1998; Naliboff et al., 2001). These have always used stimuli that are rated above the pain threshold (Silverman et al., 1997; Naliboff et al., 2001), or (in the case of non-painful stimuli) have peak activity at the junction of the affective and cognitive region of the cingulate cortex which is more dorsal to the pACC (Kern et al., 1998). Thus when the pain threshold is crossed, the subsequent greater emotive response may result in pACC activity that overrides this cognitive suppression.

Dorsolateral prefrontal cortex

The left DLPFC was activated only during mid-line back stimulation. This region incorporates processes of attention, spatial orientation and motivation to a given sensory input. Sole activation in the somatic group is consistent with other studies (Strigo et al., 2003) who similarly found activation of the left DLPFC to a somatic painful stimulus to the trunk. In their paper, Strigo et al. (2003) argue that this may reflect the differences in the coping strategies seen in the two groups (Bandler et al., 2000). This is a particularly compelling argument as the PAG has close links with the DLFPC which in turn forms a frontal network with the dorsomedial pre-frontal cortex and pACC (Vogt and Pandya, 1987). Furthermore, deactivation of the pACC was associated with deactivation of the VMPFC in the visceral group



Fig. 7. The mean PE values for the mid-cingulate (mid-ACC), posterior and anterior insula (Ant ins) cortices are shown in (a). Mean PE levels are universally, but not statistically significantly lower for visceral stimulation than somatic stimulation. The ratios of mean PE to the intensity ratings are shown in (b). Standard error bars are shown. A statistically significant difference in ratio between the two mid-line structures (rectum and mid-line back) is present for the right Ant ins cortex only (* *P*<0.05, two-tailed Student's *t*-test). A greater ratio could represent brain areas which preferentially encode visceral unpleasantness or interoception.

alone. Thus, a balance of activation/de-activation within this network may drive the differential, autonomically focused motivational and affective coping responses to the two sensory modalities.

Inferior parietal cortex

A consistent difference between the cerebral activations in response to somatic and visceral stimulation in our study was the activation of the bilateral inferior parietal cortices (BA 40) to somatic but not visceral sensation. The inferior and posterior parietal cortices are polymodal association cortices whose role in pain processing is likely to involve orientation and attention toward the stimulus (Duncan and Albanese, 2003). It is important for formation of the body image and its relation to external space. Thus its activation in the somatic but not visceral group may partially explain some of the perceptual differences (particularly spatial localization and exteroception) between the two sensory modalities.

Anterior insular cortex

The design of this experiment allows us to investigate contributions of different cortical regions to intensity and unpleasantness processing during noxious visceral and somatic stimulation. The ratio data allow us to investigate regions that proportionately encode visceral sensation/unpleasantness greater than somatic sensation/pain. The ratio of PE to intensity rating for the right anterior insula is greater for visceral stimulation (Fig. 5b) than somatic stimulation suggesting a greater contribution of this brain region to the processing of visceral stimuli, specifically encoding visceral unpleasantness. Activation of the right (and left) anterior insular cortex has been induced experimentally by faces depicting disgust (Phillips et al., 1997), recall of sad personal experiences (Mayberg et al., 1999) and negative emotion (Reiman, 1997). Furthermore, negatively emotional faces displayed at the same time as receiving esophageal stimuli have resulted in greater right anterior insular cortex activation (Phillips et al., 2003a). Thus its role in pain processing is generally accepted as encoding the emotive feelings integral to the pain experience. The marked spatial overlap of right anterior insula cortex activity across both somatic and visceral groups (Fig. 3) would suggest a common function for this region between different sensory modalities i.e. encoding unpleasantness. However, Craig (2002) has described this region as the interoceptive cortex: the cortical region encoding the physiological sense of the body (Critchley et al., 2004). It could be argued that visceral sensation, along with its autonomic significance, embodies a saliently more important interoceptive input than somatic sensation. Therefore during visceral stimulation the proportionately greater right anterior insula activity (Fig. 7b) may additionally be due to heightened interoceptive processing.

In summary, considerable spatial overlap of cortical activation in key regions within the pain matrix was observed during visceral and somatic stimulation in our study. However, relatively greater activation occurred in regions that encode spatial orientation (DLPFC and inferior parietal cortex) during somatic stimulation and emotion/ interoception (right anterior insula) during visceral stimulation. These variations are in accordance with the differences in the perceptual qualities of the two sensory modalities. The arguments presented here for these differences are speculative and require further investigation, however the greater activity in the lateral pre-frontal cortex networks is consistent with previous studies (Strigo et al., 2003), A greater understanding of the differences between visceral and somatic pain processing in normal subjects will allow better interpretation of past and future imaging studies in chronic visceral or somatic pain syndromes such as irritable bowel syndrome and fibromyalgia.

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