

## Segregation of visceral and somatosensory afferents: An fMRI and cytoarchitectonic mapping study

Simon B. Eickhoff,<sup>a,b,\*</sup> Martin Lotze,<sup>c</sup> Beate Wietek,<sup>d</sup> Katrin Amunts,<sup>a,e,f</sup>  
Paul Enck,<sup>g</sup> and Karl Zilles<sup>a,b,e</sup>

<sup>a</sup>Institut für Medizin, Research Centre Jülich, Germany

<sup>b</sup>C. and O. Vogt Institut für Brain Research, University of Düsseldorf, Germany

<sup>c</sup>Institut of Medical Psychology and Behavioural Neurobiology, University of Tübingen, Germany

<sup>d</sup>Department of General Surgery, University of Tübingen, Germany

<sup>e</sup>Brain Imaging Centre West, Research Centre Jülich, Germany

<sup>f</sup>Department of Psychiatry and Psychotherapy, RWTH Aachen University, Germany

<sup>g</sup>Department of Internal Medicine VI: Psychosomatics, University Hospitals Tübingen, Germany

Received 28 November 2005; revised 13 January 2006; accepted 20 January 2006

Available online 10 March 2006

Ano-rectal stimulation provides an important model for the processing of somatosensory and visceral sensations in the human nervous system. In spite of their anatomical proximity, the anal canal is innervated by somatosensory afferents whereas the rectum is innervated by the visceral nervous system. In a functional magnetic resonance (fMRI) experiment, we examined the cerebral responses to pneumatic balloon distension of these two structures to test whether somatosensory and visceral stimulation elicited distinct brain activations in spite of their spinal convergence. The specificity of the identified activations was analyzed by Bayesian mixed effects modeling. Activations in the parietal operculum were also compared to the location of cytoarchitectonically defined areas OP 1–4, which are part of the secondary somatosensory cortex (SII), to analyze whether the SII region was activated by anal and/or rectal stimulation.

The lowest segregation between visceral and somatosensory stimuli was in the insular cortex, which supports the interpretation of the insula as an integrative region, receiving input from different sensory modalities. The most distinct segregation was found in the frontoparietal operculum. Here the activations following anal and rectal stimulation were not only functionally but also anatomically distinct. Anal sensations were processed similar to other somatosensory stimuli in the SII cortex (area OP 4). Rectal afferents on the other hand were not processed in SII. Rather, they evoked activation at a more anterior location on the precentral operculum. These results demonstrate a

functionally and anatomically distinct processing of somatosensory and visceral afferents in the human cerebral cortex.

© 2006 Elsevier Inc. All rights reserved.

*Keywords:* Ano-rectal; Brain–gut axis; Anatomy; Parietal operculum; SII cortex; Bayesian modeling

### Introduction

Ano-rectal sensations provide an important model for the differentiation between somatosensory and visceral afferents in the human central nervous system. In spite of the close anatomical relationship between the anal canal and the distal rectum, there are clear differences in their innervation. The rectum is a visceral organ innervated by unmyelinated C-fibers and thinly myelinated A $\delta$ -fibers which ascend via the splanchnic nerves to the sacral dorsal root ganglia (Loening-Baucke et al., 1994; Sengupta and Gebhart, 1994). The anal canal, on the other hand, has a somatosensory innervation from the pudendal nerve. Consequently, anal sensation is more precise in localization and possesses a lower threshold compared to rectal perception (Golinger and Hughes, 1951).

Since perception of ano-rectal sensations is crucial for the maintenance of continence, it also plays an important role in clinical neuroscience (Whitehead et al., 1981). Two major perceptive functions are involved in the process of fecal continence: rectal sensing of its filling and anal identification of content and consistency. The maintenance of fecal continence is thus dependent on both systems described above. If one or both components are interrupted, e.g. due to spinal cord injury or systemic diseases, patients will suffer from incontinence (Golinger and Hughes, 1951; Duthie and Bennett, 1963). Moreover,

\* Corresponding author. Institut für Medizin, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany. Fax: +49 2461 61 2820.

E-mail address: S.Eickhoff@fz-juelich.de (S.B. Eickhoff).

Available online on ScienceDirect (www.sciencedirect.com).

increased sensitivity of this gastrointestinal compartment is a major pathomechanism of functional bowel disorders such as the irritable bowel syndrome. These conditions frequently also result in urge and incontinence (Naliboff et al., 2001; Bonaz, 2003; Verne et al., 2003; Mayer et al., 2005).

Previous functional neuroimaging studies have identified the parietal operculum as a key region for the processing of visceral sensations evoked by rectal or esophageal distension (Binkofski et al., 1998; Aziz et al., 2000a,b; Lotze et al., 2001; Strigo et al., 2003, 2005; Hobson et al., 2005). The parietal operculum is also the location of the secondary somatosensory cortex (SII), which consists of at least three distinct subdivisions (Kaas and Collins, 2003). The question therefore arises whether SII also sustains visceral perception. Some authors proposed that visceral and somatosensory activations in the parietal operculum are spatially separated (Aziz et al., 2000b; Lotze et al., 2001; Strigo et al., 2005). Thus, the somatosensory SII cortex might not be involved at all in the processing of visceral stimuli. This view is contradicted by studies not showing a separation between cutaneous and visceral activations (Hobday et al., 2001). The latter results imply that at least some subdivisions of SII also process input from visceral organs.

In the present study, we examined the cortical representations of somatosensory and visceral sensations by reanalyzing an fMRI experiment, which used pneumatic stimulation of the anal canal and the distal rectum (Lotze et al., 2001). Two main questions were addressed: are anal (somatosensory) and rectal (visceral) sensations processed separately in the human brain? How do the respective activations compare to the cytoarchitectonic organization of the SII region (Eickhoff et al., 2006a,b)?

## Methods

### *Subjects and stimulation*

Eight healthy subjects (four males; average age 37.3 years) with no history of neurological, psychiatric or ano-rectal illness gave informed consent. The study was approved by the ethics committee of the Medical School, University of Tübingen, Germany. After the subjects evacuated their rectum, a double-balloon catheter was inserted. One balloon was positioned in the distal rectum approximately 15 cm from the anal verge the second in the anal canal. To ensure stability the probe was fixed to the buttocks. Air inflation of the balloon was performed manually by a physician experienced with anal and rectal manometry (BW). To evoke feelings of discomfort but avoid any relevant painful stimulation, the inflation of the balloon was individually adjusted to remain just below pain threshold. The individual thresholds were tested in a separate session just prior to the fMRI recording. Two visual analogue scores were used: one for unpleasantness (0: absolutely not unpleasant; 10: maximal unpleasant) and one for pain (0: absolutely not painful; 10: unbearable painful). For rectal stimulation the balloon was preinflated with 100 ml prior to the experimental session. This condition, to which all subjects adapted rapidly, served as baseline. The necessity for a preload in the rectal baseline was imposed by the fact that the rectal filling volume was substantially higher than that of the anal canal. Therefore, some preload was necessary in order to keep the rise and decay times comparable for both type of stimulation. Since subjects reported no feelings of filling or discomfort at all during

this baseline state, we could confidently exclude any consciously arising perception. However, the possibility cannot be entirely precluded, that some tonic receptors were nevertheless activated during rest, rendering this condition really a “high-level baseline” for predominantly phasic distension receptors within the rectal wall (which of course are also innervated by the visceral nervous system). Additional volumes between 100 and 250 ml (average 173.6 ml; SD 45.0 ml) were injected for the activation periods. For stimulation of the anal canal, the balloon was completely deflated in the rest condition. For the activation periods, volumes between 7.5 and 25 ml (average 15.5 ml, SD 7.7 ml) were injected. The fMRI paradigm consisted of four sessions of 16 stimulation cycles. Each cycle consisted of approximately 3 s stimulation followed 18 s rest. The distal rectum was stimulated during half of the sessions, the anal canal during the other half. The order of the experimental sessions was pseudo-randomized across subjects.

### *fMRI procedure and image preprocessing*

Functional MR images were acquired on a Siemens Vision 1.5 T whole-body scanner (Erlangen, Germany) using blood-oxygen-level-dependent (BOLD) contrast (Gradient-echo EPI pulse sequence, TR = 3 s, in plane resolution =  $3 \times 3$  mm, slice thickness 4 mm, 28 axial slices for whole-brain coverage). Each session consisted of 112 images preceded by two dummy images allowing the MR scanner to reach a steady state. These were discarded prior to analysis. Additional high-resolution anatomical images (voxel size  $1.5 \times 1 \times 1$  mm<sup>3</sup>) were acquired using a standard T1-weighted 3D MP-RAGE sequence. Images were analyzed on a Pentium 4 Windows XP system using SPM2 (<http://www.fil.ion.ucl.ac.uk/spm>). The EPI images were corrected for head movement between scans by an affine registration (Ashburner and Friston, 2003c). The T1 scan was coregistered to the mean of the realigned EPIs. Subsequently, it was spatially normalized to the MNI single subject template (Evans et al., 1992; Collins et al., 1994; Holmes et al., 1998) using linear proportions and a nonlinear sampling algorithm (Ashburner and Friston, 2003a,b). The resulting normalization parameters were then applied to the EPI volumes. These were hereby transformed into standard stereotaxic space and resampled at  $2 \times 2 \times 2$  mm<sup>3</sup> voxel size. The normalized images were spatially smoothed using an 8-mm FWHM Gaussian kernel to meet the statistical requirements of the General Linear Model and to compensate for residual anatomical variations across subjects.

### *Statistical analysis*

The data were analyzed in the context of the general linear model employed by SPM2. Each experimental condition was modeled using a boxcar reference vector convolved with a canonical hemodynamic response function. Low-frequency signal drifts were filtered using a set of discrete cosine functions with a cut-off period of 42s. Temporal autocorrelations between scans were estimated using a first-order autoregressive model. Parameter estimates were subsequently calculated for each voxel using weighted least squares to provide maximum likelihood estimators based on the nonsphericity of the data (Kiebel and Holmes, 2003). The weighting ‘whitens’ the errors rendering them identically and independently distributed. No global scaling was applied.

The main effects of anal and rectal stimulation were computed by applying appropriate baseline contrasts. The corresponding contrast from different subjects was then analyzed in a second level Bayesian mixed effects model to allow inference to the general population (Penny and Holmes, 2003). For this model, we used the probabilistic empirical Bayes algorithm implemented in SPM2. This algorithm calculates the conditional distribution for the parameter estimates (across subjects) at each voxel using the variance across voxels as Bayesian prior (Friston, 2002; Friston et al., 2002a,b; Friston and Penny, 2003a,b). The resulting posterior probability maps were thresholded at a probability of 0.95 for an effect size greater than the prior standard deviation ( $\gamma$  threshold). That is, only those voxels were considered active, whose parameter estimates were larger than  $\gamma$  with at least 95% confidence. The rationale for using the prior standard deviation as the effect size threshold  $\gamma$  is that it equates to a “background noise level”. That is, it represents the level of activation that is generic to the brain as a whole. The chosen threshold thus allows directing Bayesian inference to only show those voxels that are almost certainly more active than this generic response (Friston and Penny, 2003a,b). Since Bayesian modeling allows the estimation of conditional probabilities for the existence of activation given the data, it cannot only be used to declare brain regions as active with a quantifiable confidence. Rather, it can also quantify the likelihood for the absence of activation (Friston and Penny, 2003a,b). This allows the

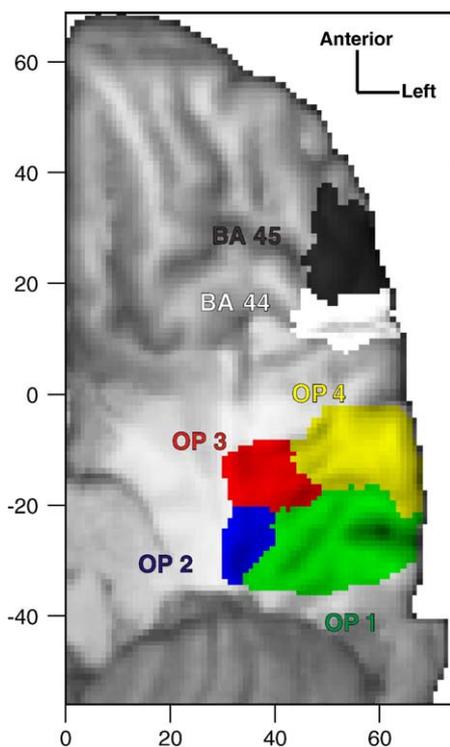


Fig. 1. The cytoarchitectonic organization of the human fronto-parietal operculum, shown as a maximum probability map (MPM) projected onto a surface rendering of the MNI single subject template. The temporal lobes were removed for display purposes. In the parietal operculum, four distinct architectonic areas (OP 1–OP 4) can be identified. OP 1 is the human analogue of area SII in nonhuman primates (not to be confused with the whole “SII region”), OP 4 corresponds to monkey area PV, whereas OP 3 constitutes the human equivalent of area VS. OP 2 finally is not part of the SII cortex, but the human analogue of the primate parietal-insular vestibular cortex (Eickhoff et al., 2006a,b, in press).

examination of functional specificities and dissociations via the computation of likelihood ratios as described below. In classical inference, on the other hand, the  $P$  values only give the probability of observing the measured data by chance in an infinite number of experiments, without permitting statements on the probability for genuine activation.

To obtain unbiased estimates for the functional specificity of the identified activations, we compared the posterior probabilities for *both* conditions within each activated cluster. For example, for a cluster active following rectal stimulation, the posterior probability for rectal activation was expressed relative to the posterior probability for anal activation. This likelihood ratio (LR) indicates the confidence in the presence of activation in the preferred condition, relative to the confidence in the presence of activation following the nonpreferred condition. A high LR thus corresponds to a high degree of functional specificity, whereas a low LR can be expected for brain regions, which respond similarly to both stimulation paradigms. The product of the likelihood ratios for (spatially) corresponding clusters defined by different conditions (e.g. the LR of the insular activation following rectal stimulation multiplied by the LR of the insular activation following anal stimulation) can then be used to quantify the segregation of somatosensory and visceral processing in a particular brain region. This product, which is subsequently referred to as “functional segregation”, is simply equivalent to the likelihood ratio of the conjoint probability for the preferred vs. that for the nonpreferred condition.

#### Comparison with cytoarchitectonic data

The localization of the functional activations with respect to cytoarchitectonic areas was analyzed based on the maximum probability map (MPM, Fig. 1). This map denotes the most likely anatomical area at each voxel of the MNI single subject template (Eickhoff et al., 2005). The definition of such MPMs is based on probabilistic cytoarchitectonic maps derived from the analysis of cortical areas in a sample of 10 human post-mortem brains, which were subsequently normalized to the MNI reference space. The significant results of the random effects analysis were compared both to the MPM and the individual probabilistic maps of the parietal operculum (Eickhoff et al., 2006a) using the SPM Anatomy toolbox ([http://www.fz-juelich.de/ime/spm\\_anatomy\\_toolbox](http://www.fz-juelich.de/ime/spm_anatomy_toolbox)) (Eickhoff et al., 2005).

## Results

### Behavioral results

Upon debriefing, all subjects reported a feeling of gas and stool pressure elicited by the stimulation. This sensation was always well perceivable. Subjects rated the pain intensity during stimulation with 0.3 ( $\pm 0.17$ ) in average on a scale from 0–10. The unpleasantness scores during rectal (mean score of  $5.24 \pm 2.36$  SD) and anal stimulation ( $4.76 \pm 2.23$ ) did not differ significantly ( $t = 0.46$ ;  $P = 0.67$ ; n.s.). These behavioral measures indicate that the stimulation protocol was successful in excluding two potential confounds: there was no difference in unpleasantness, which might have led to differential activation in areas involved in affective or emotional processing. Pain-related activation can also be largely excluded as subjects explicitly denied

Table 1  
Location of significant clusters of activation following anal and rectal pneumatic stimulation

	Cluster location		Local maxima	
	Macroanatomy	Cytoarchitecture	<i>x, y, z</i>	Cytoarchitectonic probabilities
<i>a) Main effect of anal canal stimulation</i>				
1	L parietal operculum	OP 4: 97%	−54/−12/18	OP 4: 70% [60–80%] OP 3: 20% [0–20%] OP 1: 20% [0–20%]
2	Mesencephalon	None	6/−22/−6	Nil
3	L anterior insula	None	−42/2/−6	Nil
<i>b) Main effect of rectal stimulation</i>				
1	L precentral operculum	OP 4: 19% BA 44: 7%	−62/4/10	BA 44: 30% [10–50%] OP 4: 20% [0–20%]
2	Mesencephalon	None	−2/−12/4	Nil
3	L thalamus	None	−6/−28/6	Nil
4	R pallidum	None	20/6/6	Nil
5	L anterior insula	OP 3: 2%	−44/−12/4	Nil

(a) Relative increases in brain activity resulting from stimulation of the anal canal (somatosensory stimulation). (b) Relative increases in brain activity resulting from the stimulation of the distal rectum (visceral stimulation).

All coordinates in anatomical MNI space. The number of each activation cluster corresponds to the number used to label the foci in Fig. 2.

relevant painful sensations. Differences in the response patterns following anal and rectal stimulation can therefore be considered to reflect genuine differences in the processing of somatosensory and visceral stimuli.

#### Neural activations

Pneumatic stimulation of the anal canal activated the left parietal operculum, the left anterior insula and the ventral midbrain (Table 1a, Fig. 2). Rectal stimulation elicited significant changes in the BOLD signal in left precentral operculum, the left anterior insular, the ventral midbrain, the left thalamus and the pallidum (Table 1b, Fig. 2). Thus, in spite of the different peripheral innervation, both rectal and anal stimulation evoked activation in comparable brain regions, namely the ventral

midbrain, the left insular cortex and the left fronto-parietal operculum.

In contrast to previous studies of ano-rectal sensations, we did not observe activation in the primary somatosensory cortices, motor areas, the anterior cingulate cortex and the right operculum. More precisely, no activation in those regions was sufficiently robust to be declared active in our conservative but theoretically motivated thresholding procedure. On a more lenient threshold (posterior probability of >50% for any activation), all of these regions showed some evidence for activation alongside several other sites on both hemispheres (e.g. the inferior parietal cortex, the cerebellum and the dorsolateral prefrontal cortex). However, these responses were either too weak or too variable to be declared active with sufficient confidence. In the following, we will therefore focus on

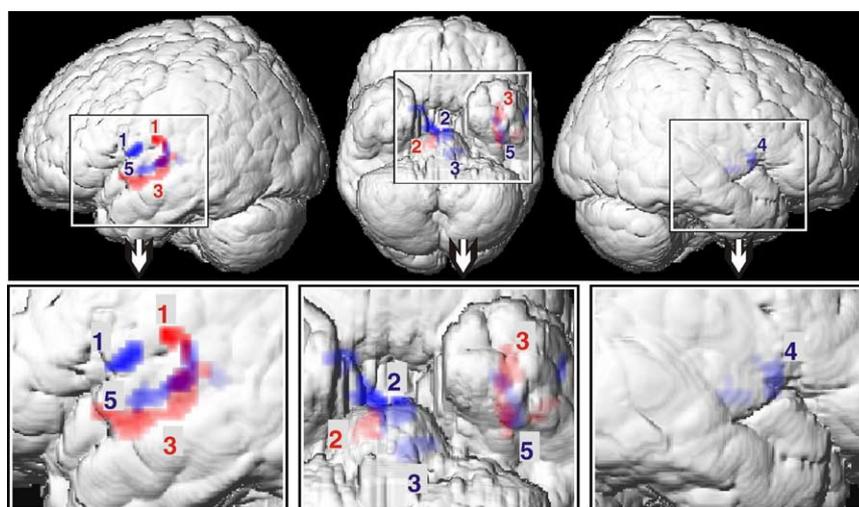


Fig. 2. (Upper row) Foci associated with the processing of anal (red) and rectal (blue) sensations. Areas of significant increase in BOLD signal (95% confidence for activation greater than the background noise) are shown superimposed on a surface rendering of the MNI single subject template. (Lower row) Detail views on these renderings. The location of the detail images is denoted by the black and white boxes in the upper row of images. The exact coordinates and the height of the local maxima within the areas of activation as well as quantitative descriptions (probabilities) of their cytoarchitectonic assignments are given in Table 1. The red numbers in the figure point to the respective cluster label in Table 1a (effects of anal stimulation) while the blue numbers point to the respective cluster label in Table 1b (effects of rectal stimulation).

examining whether the described significant activations following anal and rectal stimulation (see Table 1 and Fig. 2) are functionally and anatomically distinct or not.

#### Subcortical activations

Both stimulations evoked significant activation in the ventral midbrain. These activations were clearly spatially separated from each other (Fig. 3A) and there was no overlap between them. The posterior probabilities for a significant effect of anal or rectal stimulation within their respective clusters given the measured data (posterior probabilities) were close to 100%. The posterior probabilities for activation following the nonpreferred condition, however, revealed a functional dissociation of these foci: within the cluster responsive to rectal stimulation, the mean posterior probability for an effect of anal stimulation was 62%. In contradistinction, the mean posterior probability for an effect of rectal stimulation within the anal activation cluster was only 21%. The likelihood ratio (LR) was 1.6 for the rectal and 4.6 for the anal cluster. Pneumatic stimulation of the distal rectum also resulted in two further subcortical clusters of activation in the left thalamus (LR: 2.0) and the right pallidum. This latter cluster was highly specific to rectal stimulation (LR: 3.8).

#### Cortical activations

In contrast to the subcortical activations, the insular activations overlapped by 14% (anal) and 22% (rectal) of their respective volumes (Fig. 3B). The weaker separation between somatosensory

and visceral processing in the insular cortex was confirmed by the Bayesian analysis: the probability for an effect of anal stimulation within the rectal activation was 77% (LR 1.3) while the probability for an effect of rectal stimulation within the anal activation cluster was 44% (LR 2.2).

The two clusters on the fronto-parietal operculum, on the other hand, were clearly separated from each other by a distance of about 1.5 cm (Fig. 4). Moreover, the functional segregation between somatosensory and visceral processing was also more pronounced compared to the segregation in the midbrain or the insula: the posterior probability for an effect of anal stimulation in the rectal activation cluster was 39% (LR: 2.5). The posterior probability for an effect of rectal stimulation in the anal activation cluster was 28% (LR: 3.5).

#### Functional segregation of somatosensory and visceral afferents

The functional specificity of the anal activations was generally higher than that of the rectal activations in all three examined brain regions (Table 2). That is, those neuronal modules that process somatosensory afferents were generally more specific to this task than modules sustaining the perception of visceral sensations. The latter in turn do more likely also respond to stimulation of the somatosensory innervated anal canal.

However, there were also differences in the functional specificity between the three regions: in the ventral midbrain, the anal activation was highly specific to somatosensory stimulation whereas the neighboring rectal activation cluster had a much lower functional specificity. In the insular cortex, both somatosensory

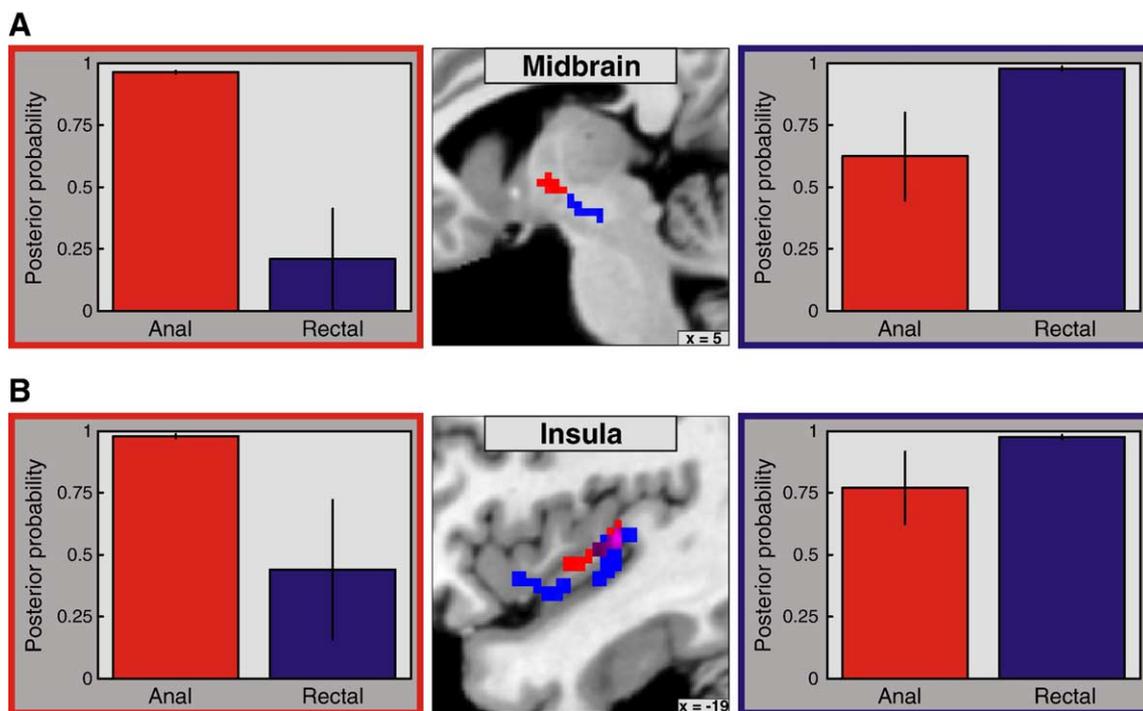


Fig. 3. Functional separation between the processing of anal and rectal afferents in the midbrain (A) and the insula (B). (Middle panel) Sagittal sections through the MNI single subject template at  $x = 5$  (top) and  $x = -19$  (bottom). The activation cluster for anal stimulation is shown in red; that for rectal stimulation is shown in blue. (Left panel) Mean posterior probabilities for activations following anal (red) and rectal (blue) stimulation, in the midbrain (top) and insular (bottom) clusters significantly associated with the processing of anal afferents. (Right panel) Mean posterior probabilities for activations following anal (red) and rectal (blue) stimulation, in the midbrain (top) and insular (bottom) clusters significantly associated with the processing of rectal afferents.

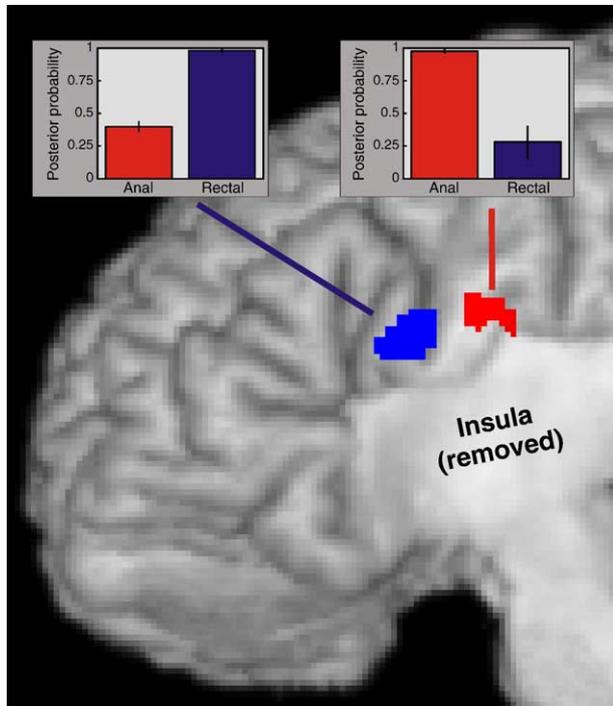


Fig. 4. Functional separation of anal and rectal processing on the fronto-parietal operculum. The significant (95% confidence for activation greater than the background noise level) activation clusters for both conditions are displayed on a surface rendering of the MNI single subject template (temporal lobe removed). The smaller diagrams show the mean posterior probabilities for activation following anal (red) and rectal (blue) stimulation in the two clusters. These two clusters are spatially well separated from each other and show a high degree of functional specificity.

and viscerally evoked activations were largely unspecific. This weak functional segregation corresponded well to the lack of spatial distinction between the two activated clusters (Fig. 3B). The highest functional segregation was observed for the fronto-parietal operculum. Here anal and rectal stimulation resulted in

two distinct clusters. These clusters showed a good spatial separation and a high specificity for the respective stimulation modality.

#### Comparison with cytoarchitectonic data

The comparison of the two opercular activations with the probabilistic cytoarchitectonic maps of OP 1–4 (Fig. 5) revealed that the activation following stimulation of the anal canal was located almost exclusively (97% of the cluster volume) in area OP 4. The mean probability for OP 4 in the activated voxels was 54%. At the location of the local maximum, the probability for OP 4 was 70% (60–80% for the surrounding voxels). The second most likely cytoarchitectonic area at the location of the local maximum was OP 3. Its probability, however, was only 20% (0–20% for the surrounding voxels). Therefore, this activation can be assigned with high confidence to area OP 4. In contradistinction, only 19% of the rectal activation was located in OP 4 (mean probability for OP 4: 13%). 7% of the cluster was allocated to BA 44 (Amunts et al., 1999). The majority of its volume, however, was located in the yet unmapped precentral opercular cortex between OP 4 and BA 44. At the location of the local maximum for the effect of rectal distension, BA 44 was found with a probability of 30% (10–50%) while OP 4 was found with a probability of 20% (0–20%). Thus, the anatomical location of the activation evoked by rectal distension was most likely not OP 4 but the (as of today) unmapped precentral opercular cortex between this area and BA 44.

#### Discussion

We have used pneumatic distension of the anal canal and the distal rectum to investigate the brain regions involved in somatosensory and visceral processing. The particular focus of this study was whether these stimuli evoke functionally and anatomically distinct brain activations. To address this question, we used methods recently introduced into functional neuroimaging:

Table 2

Functional specificity of the activation foci identified for the processing of anal and rectal stimulation

	$P_{(RID)}$	$P_{(AID)}$	Likelihood ratio	Functional segregation
Midbrain				
Anal cluster	21.0%	96.4%	4.6	7.36
Rectal cluster	97.8%	62.4%	1.6	
Thalamus				
Rectal cluster	97.4%	49.6%	2.0	
Pallidum				
Rectal cluster	97.3%	25.6%	3.8	
Insula				
Anal cluster	97.9%	43.9%	2.2	2.86
Rectal cluster	77.0%	97.6%	1.3	
Fronto-parietal operculum				
Anal cluster	27.9%	97.7%	3.5	8.75
Rectal cluster	99.0%	39.1%	2.5	

The posterior probability given the observed data is shown for both experimental conditions for each cluster of activation ( $P_{(RID)}$ : posterior probability for an effect of rectal stimulation,  $P_{(AID)}$ : posterior probability for an effect of anal stimulation).

The likelihood ratio (LR, computed with respect to the condition used to define the activation cluster) gives an unbiased estimate of the functional specificity of the observed activation. Higher specificities for one type of stimulation correspond to higher likelihood ratios, and vice-versa. For those brain regions, where activation foci were observed for both conditions, the functional segregation was quantified by the product of the likelihood ratios for the anal and the rectal activation cluster.

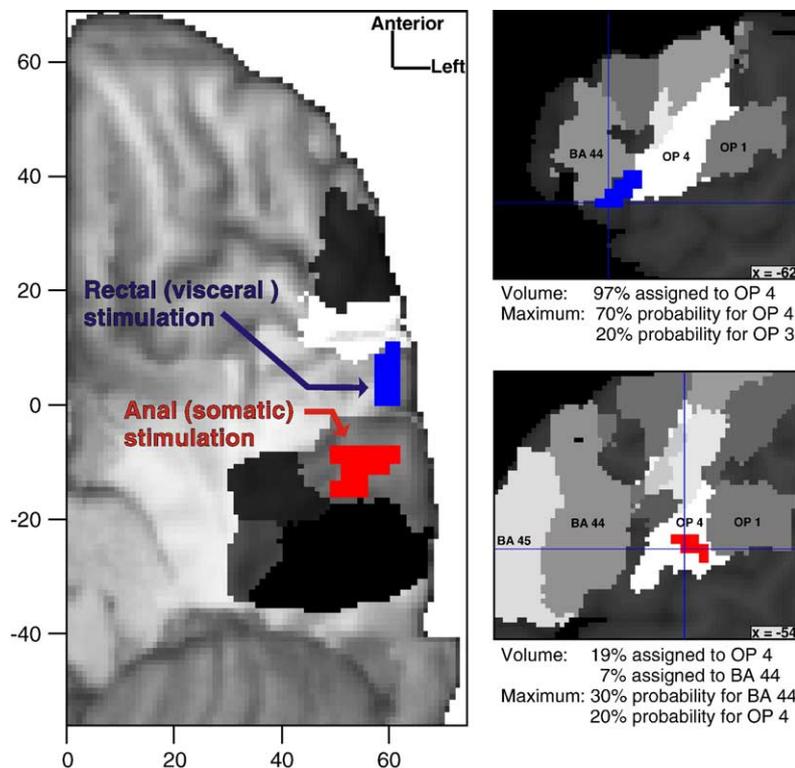


Fig. 5. (Left image) Comparison of the opercular activations following anal and rectal stimulations with the maximum probability map (MPM) of OP 1–4 and BA 44 + 45 (shown as a projection onto the surface rendering of the MNI single subject template, cf. Fig. 1). Note that the significant clusters are clearly separated from each other. Moreover, they are also located in different cytoarchitectonic areas: The location of the activity following anal stimulation corresponds mainly to OP 4, whereas the activation cluster resulting from the stimulation of the distal rectum is located anterior to OP 4, between this area and BA 44. (Right images) Sagittal sections through the locations of the local maxima of the opercular activations following rectal (upper image) and anal (lower image) stimulation. The extent of the different cytoarchitectonically defined areas is marked by different grey values; the MNI single subject template is shown in the background.

Bayesian random effects modeling (Friston et al., 2002a,b) and a comparison with probabilistic cytoarchitectonic maps (Eickhoff et al., 2005). Hereby, we demonstrated that the functional specificity for somatosensory and visceral processing varied across cortical and subcortical brain regions. It was lowest in the insular cortex, while the highest functional segregation was found in the frontoparietal operculum. Moreover, these opercular activation foci were not only functionally but also anatomically distinct. The response to anal stimulation was allocated with high confidence to parietal opercular area OP 4 (Eickhoff et al., 2006a,b) whereas the response to anal stimulation is located more anterior on the precentral operculum between OP 4 and BA 44.

#### Stimulation specificity

The ano-rectal region provides an important model for the differentiation of somatosensory and visceral afferents in the human central nervous system, since the anal canal and the distal rectum are adjacent but neurologically distinct: rectal stimulation engages visceral afferents whereas anal stimulation engages predominantly somatosensory afferents. Although these stimuli have repeatedly and successfully been used in neuroimaging experiments before (Loening-Baucke and Yamada, 1993; Baciú et al., 1999; Kern et al., 2001; Lotze et al., 2001; Kern and Shaker, 2002; Drewes et al., 2004; Dunckley et al., 2005), some potential confounds inherent to ano-rectal stimulation have to be acknowledged.

Firstly, the most proximal part of the anal canal has in part a dual innervation since it also consists of smooth muscles. Therefore, pneumatic distension of the anal canal might also stimulate some visceral afferents. However, since we only stimulated the distal part of the anal canal near the sphincter and the locations of anal and rectal stimulation were always more than 10 cm apart from each other, an overlap of visceral and somatosensory stimulation is highly unlikely. Furthermore, the presence of partially overlapping input can also be largely excluded by our fMRI data: both anal and rectal stimulation resulted in highly specific activations in several brain regions. This existence of distinct central responses to each condition renders the likelihood of a peripheral signal, which is a-priori intermingled (due to a significant stimulation of both visceral and somatosensory afferents in one of the two conditions), very small.

Secondly, anal stimulation might provoke contraction of the external anal sphincter due to a reflexive but voluntary increase of its tonus. This would in turn lead to confounding activation in motor-related brain structures. In the presented random effects analysis, however, no area known to be involved in cortical motor control (i.e. M1, SMA, frontal premotor cortex, etc.) could be declared active above generic background noise with sufficient confidence. In fact, the only significant frontal activation was observed on the precentral operculum. This cluster, however, was highly specific to rectal stimulation during which a coactivation of motor structures would not be expected. The corresponding activation evoked by anal stimulation, on the other hand, was

distinctly located more posterior in the secondary somatosensory cortex.

Additional confounds might have been caused by the hand held syringe for mechanical stimulation, which does not allow to time the in- and deflation as exact as possible with automated pumps. Although the stimulation was always performed by the same experimenter and every attempt was taken to keep these times as constant as possible, they might have differed between subjects, runs and individual stimulations. These differences would then, however, be nonsystematically and should therefore not interact with the observed results.

Finally, a 100-ml preload was needed in the rectal stimulation condition due to the substantially higher rectal filling volume. Subjects reported no conscious feelings of filling or discomfort at all during this state. Nevertheless, some tonic receptors may have been activated during rest, rendering the difference in the activation condition predominantly a response of phasic distension receptors. It is important to highlight, however, that this represents no confound to the main objective of this study, i.e. the functional and anatomical comparison between somatosensory and visceral afferents. As both phasic and tonic receptors in the rectal wall are innervated by the visceral nervous system, this comparison is not related to the extent, to which the rectal stimulation is composed of phasic and tonic signals.

#### *Segregation and convergence of visceral and somatosensory input*

The well known convergence of visceral and somatosensory afferents in the dorsal root ganglia of the spinal cord forms the neurophysiological basis for the referral of visceral pain to somatosensory structures (Loening-Baucke et al., 1994; Sengupta and Gebhart, 1994; Langhorst et al., 1996; Ladabaum et al., 2000; Fink, 2005). In spite of this convergence, we demonstrated in this study that rectal (i.e. visceral) sensations are distinctly processed for anal (i.e. somatosensory) perceptions in human brain. Up to now, different activation patterns following visceral and somatosensory stimulation have predominantly been described in brain areas known to be involved in processing affect or pain (e.g. the anterior cingulate cortex or the orbitofrontal cortex) rather than in sensory cortices (Aziz et al., 2000a). These activations, however, might reflect confounding effects of e.g. unpleasantness rather than genuine differences in sensory processing. In the present study, however, we did not observe activation of brain areas commonly associated with pain processing or affective reactions. This is in agreement to our behavioral data that indicated no difference in affective rating and no relevant experience of pain. The observed differences in the activation patterns should therefore reflect genuine differences in the cerebral processing of somatosensory and visceral afferents.

The functional segregation between visceral and somatosensory activations is not equal throughout the brain. They are clearly separated in the fronto-parietal operculum and the midbrain. This indicates that distinct brain modules are devoted to the processing of visceral afferents at both cortical and subcortical level. This distinction between visceral and somatosensory activations is lacking in the insular cortex. Our results therefore support the interpretation of the insula as an integrative region which receives input from different sensory modalities (Binkofski et al., 1998; Banzett et al., 2000; Lotze et al., 2001; Bamiou et al., 2003; Stephan et al., 2003; Critchley et al., 2004;

Vandenbergh et al., 2005; Yaguez et al., 2005). Moreover, this observation is also in line with the notion that the insular cortex combines different information about the body's state and creates an interoceptive awareness (Augustine, 1985; Craig, 2002, 2003; Cameron and Minoshima, 2002; Critchley et al., 2004).

#### *The role of SII in the processing of ano-rectal afferents*

The involvement of the fronto-parietal operculum in the processing of somatosensory and visceral sensations has previously been described using fMRI (Binkofski et al., 1998; King et al., 1999; Aziz et al., 2000b; Kern and Shaker, 2002; Strigo et al., 2005), PET (Rosen et al., 1994; Ladabaum et al., 2001; Stephan et al., 2003; Vandenbergh et al., 2005) and EEG/MEG (Loening-Baucke and Yamada, 1993; Loening-Baucke et al., 1994; Schnitzler et al., 1999; Hobson et al., 2005). Since the localization of the human SII cortex in the parietal operculum is well established (Burton et al., 1993; Disbrow et al., 2000; Ruben et al., 2001; Zilles et al., 2003; Kaas and Collins, 2003), most studies consequently have interpreted these opercular activation foci as belonging to "SII". The concept of the SII region, however, has changed dramatically over the last decade. The current view on this region in primates (including humans) is mainly based on histological, electrophysiological and connectivity studies carried out in several monkey species (Krubitzer and Kaas, 1990; Krubitzer et al., 1995; Burton et al., 1995; Disbrow et al., 2003). The results of these studies coherently suggest the existence of several anatomically and functionally distinct areas in the parietal operculum: areas SII (posterior) and PV (anterior) represent the core areas of the SII cortex. Area VS is located more medially to these areas (Cusick et al., 1989; Wu and Kaas, 2003; Kaas and Collins, 2003).

A recent study of our own group identified four distinct cytoarchitectonic areas (termed OP 1–4) on the human parietal operculum (Zilles et al., 2003; Eickhoff et al., 2006b). Three of these appear equivalent to SII subregions in monkeys based on their topology and a meta-analysis of functional imaging studies (Eickhoff et al., 2006a). More precisely, OP 1 seems to be equivalent to area SII, OP 4 to area PV, and OP 3 to area VS. OP 2 finally is not a part of the SII region but the putative analogue of the primate parietal-insular vestibular cortex (Eickhoff et al., *in press*).

Our current results show that anal sensations were specifically processed in OP 4, i.e. human area PV. That is to say, anal afferents were processed in the same cytoarchitectonic area as somatosensory input from other body parts like hands (Young et al., 2004; Naito et al., 2005; Grefkes et al., 2005; Eickhoff et al., 2006a), feet (Young et al., 2004) or external genitals (Kell et al., 2005). Thus, there seems to be no fundamental difference in the central processing of sensations from the anal canal mucosa and those from the skin of, e.g. the hands. However, our data contradicts the notion that SII is also involved in the processing of visceral stimuli. Rather, this function appears to be located more anterior on the precentral operculum between OP 4 and BA 44. Our observation that visceral activation is located outside of the "SII cortex" provides further support for the existence of multiple anatomically and functionally distinct areas on the fronto-parietal operculum. It is thus well in line with a growing amount of data from both humans and nonhuman primates showing that different parts of the parietal operculum have different func-

tional properties, architecture and connectivity patterns (Krubitzer and Kaas, 1990; Krubitzer et al., 1993; Burton and Sinclair, 2000; Burton et al., 1997, 1999; Qi et al., 2002; Disbrow et al., 2003). Consequently, we may argue that the functional description “SII” and the anatomical label “parietal operculum” cannot be treated as equivalent.

### Summary and conclusions

The separation between the cortical processing of visceral and somatosensory stimuli is lowest in the insular cortex, which seems to play an integrative role for a variety of sensory processes. This separation is most pronounced in the fronto-parietal operculum. Here the activations following anal and rectal stimulation are also anatomically distinct. More specifically, anal sensations are processed in area OP 4 similar to other somatosensory stimuli. Rectal afferents on the other hand are not processed in SII but more anterior on the precentral operculum. These results demonstrate for the first time a functionally and anatomically distinct processing of somatosensory and visceral afferents in the human brain in spite of their partial convergence at the level of the spinal cord.

### Acknowledgments

This Human Brain Project/Neuroinformatics research was funded jointly by the National Institute of Mental Health, of Neurological Disorders and Stroke, of Drug Abuse, the National Cancer Centre and the Deutsche Forschungsgemeinschaft (KFO-112; EN 50/18).

### References

- Amunts, K., Schleicher, A., Burgel, U., Mohlberg, H., Uylings, H.B., Zilles, K., 1999. Broca's region revisited: cytoarchitecture and intersubject variability. *J. Comp. Neurol.* 412, 319–341.
- Ashburner, J., Friston, K.J., 2003a. Spatial normalization using basis functions. In: Frackowiak, R.S., Friston, K.J., Frith, C.D., Dolan, R.J., Price, C.J., Ashburner, J., Penny, W.D., Zeki, S. (Eds.), *Human Brain Function*. Academic Press.
- Ashburner, J., Friston, K.J., 2003b. High-dimensional image warping. In: Frackowiak, R.S., Friston, K.J., Frith, C.D., Dolan, R.J., Price, C.J., Ashburner, J., Penny, W.D., Zeki, S. (Eds.), *Human Brain Function*. Academic Press.
- Ashburner, J., Friston, K.J., 2003c. Rigid body registration. In: Frackowiak, R.S., Friston, K.J., Frith, C.D., Dolan, R.J., Price, C.J., Ashburner, J., Penny, W.D., Zeki, S. (Eds.), *Human Brain Function*. Academic Press.
- Augustine, J.R., 1985. The insular lobe in primates including humans. *Neurol. Res.* 7, 2–10.
- Aziz, Q., Schnitzler, A., Enck, P., 2000a. Functional neuroimaging of visceral sensation. *J. Clin. Neurophysiol.* 17, 604–612.
- Aziz, Q., Thompson, D.G., Ng, V.W., Hamdy, S., Sarkar, S., Brammer, M.J., Bullmore, E.T., Hobson, A., Tracey, I., Gregory, L., Simmons, A., Williams, S.C., 2000b. Cortical processing of human somatic and visceral sensation. *J. Neurosci.* 20, 2657–2663.
- Baciu, M.V., Bonaz, B.L., Papillon, E., Bost, R.A., Le Bas, J.F., Fournet, J., Segebarth, C.M., 1999. Central processing of rectal pain: a functional MR imaging study. *Am. J. Neuroradiol.* 20, 1920–1924.
- Bamiou, D.E., Musiek, F.E., Luxon, L.M., 2003. The insula (Island of Reil) and its role in auditory processing. Literature review. *Brain Res. Brain Res. Rev.* 42, 143–154.
- Banzett, R.B., Mulnier, H.E., Murphy, K., Rosen, S.D., Wise, R.J., Adams, L., 2000. Breathlessness in humans activates insular cortex. *NeuroReport* 11, 2117–2120.
- Binkofski, F., Schnitzler, A., Enck, P., Frieling, T., Posse, S., Seitz, R.J., Freund, H.J., 1998. Somatic and limbic cortex activation in esophageal distention: a functional magnetic resonance imaging study. *Ann. Neurol.* 44, 811–815.
- Bonaz, B., 2003. Visceral sensitivity perturbation integration in the brain–gut axis in functional digestive disorders. *J. Physiol. Pharmacol.* 54 (Suppl. 4), 27–42.
- Burton, H., Sinclair, R.J., 2000. Attending to and remembering tactile stimuli: a review of brain imaging data and single-neuron responses. *J. Clin. Neurophysiol.* 17, 575–591.
- Burton, H., Videen, T.O., Raichle, M.E., 1993. Tactile-vibration-activated foci in insular and parietal-opercular cortex studied with positron emission tomography: mapping the second somatosensory area in humans. *Somatosens. Motor Res.* 10, 297–308.
- Burton, H., Fabri, M., Alloway, K., 1995. Cortical areas within the lateral sulcus connected to cutaneous representations in areas 3b and 1: a revised interpretation of the second somatosensory area in macaque monkeys. *J. Comp. Neurol.* 355, 539–562.
- Burton, H., MacLeod, A.M., Videen, T.O., Raichle, M.E., 1997. Multiple foci in parietal and frontal cortex activated by rubbing embossed grating patterns across fingerpads: a positron emission tomography study in humans. *Cereb. Cortex* 7, 3–17.
- Burton, H., Abend, N.S., MacLeod, A.M., Sinclair, R.J., Snyder, A.Z., Raichle, M.E., 1999. Tactile attention tasks enhance activation in somatosensory regions of parietal cortex: a positron emission tomography study. *Cereb. Cortex* 9, 662–674.
- Cameron, O.G., Minoshima, S., 2002. Regional brain activation due to pharmacologically induced adrenergic interoceptive stimulation in humans. *Psychosom. Med.* 64, 851–861.
- Collins, D.L., Neelin, P., Peters, T.M., Evans, A.C., 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J. Comput. Assist. Tomogr.* 18, 192–205.
- Craig, A.D., 2002. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat. Rev., Neurosci.* 3, 655–666.
- Craig, A.D., 2003. Interoception: the sense of the physiological condition of the body. *Curr. Opin. Neurobiol.* 13, 500–505.
- Critchley, H.D., Wiens, S., Rotshtein, P., Ohman, A., Dolan, R.J., 2004. Neural systems supporting interoceptive awareness. *Nat. Neurosci.* 7, 189–195.
- Cusick, C.G., Wall, J.T., Felleman, D.J., Kaas, J.H., 1989. Somatotopic organization of the lateral sulcus of owl monkeys: area 3b, S-II, and a ventral somatosensory area. *J. Comp. Neurol.* 282, 169–190.
- Disbrow, E., Roberts, T., Krubitzer, L., 2000. Somatotopic organization of cortical fields in the lateral sulcus of *Homo sapiens*: evidence for SII and PV. *J. Comp. Neurol.* 418, 1–21.
- Disbrow, E., Litinas, E., Recanzone, G.H., Padberg, J., Krubitzer, L., 2003. Cortical connections of the second somatosensory area and the parietal ventral area in macaque monkeys. *J. Comp. Neurol.* 462, 382–399.
- Drewes, A.M., Rossel, P., Le Pera, D., Arendt-Nielsen, L., Valeriani, M., 2004. Dipolar source modelling of brain potentials evoked by painful electrical stimulation of the human sigmoid colon. *Neurosci. Lett.* 358, 45–48.
- Dunckley, P., Wise, R.G., Aziz, Q., Painter, D., Brooks, J., Tracey, I., Chang, L., 2005. Cortical processing of visceral and somatic stimulation: differentiating pain intensity from unpleasantness. *Neuroscience* 133, 533–542.
- Duthie, H.L., Bennett, R.C., 1963. The relation of sensation in the anal canal to the functional anal sphincter: a possible factor in anal continence. *Gut* 4, 179–182.
- Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *NeuroImage* 25, 1325–1335.

- Eickhoff, S.B., Amunts, K., Mohlberg, H., Zilles, K., 2006a. The human parietal operculum: II. Stereotaxic maps and correlation with functional imaging results. *Cereb. Cortex* 16, 268–279.
- Eickhoff, S.B., Schleicher, A., Zilles, K., Amunts, K., 2006b. The human parietal operculum: I. Cytoarchitectonic mapping of subdivisions. *Cereb. Cortex* 16, 254–267.
- Eickhoff, S.B., Weiss, P.H., Amunts, K., Fink, G.R., Zilles, K., in press. Identifying human parietal-insular vestibular cortex using fMRI and cytoarchitectonic mapping. *Hum. Brain Mapp.*
- Evans, A.C., Marrett, S., Neelin, P., Collins, L., Worsley, K., Dai, W., Milot, S., Meyer, E., Bub, D., 1992. Anatomical mapping of functional activation in stereotaxic coordinate space. *NeuroImage* 1, 43–53.
- Fink Jr., W.A., 2005. The pathophysiology of acute pain. *Emerg. Med. Clin. North Am.* 23, 277–284.
- Friston, K.J., 2002. Bayesian estimation of dynamical systems: an application to fMRI. *NeuroImage* 16, 513–530.
- Friston, K.J., Penny, W.D., 2003a. Classical and Bayesian inference. In: Frackowiak, R.S., Friston, K.J., Frith, C.D., Dolan, R.J., Price, C.J., Ashburner, J., Penny, W.D., Zeki, S. (Eds.), *Human Brain Function*. Academic Press.
- Friston, K.J., Penny, W.D., 2003b. Posterior probability maps and SPMs. *NeuroImage* 19, 1240–1249.
- Friston, K.J., Glaser, D.E., Henson, R.N., Kiebel, S., Phillips, C., Ashburner, J., 2002a. Classical and Bayesian inference in neuroimaging: applications. *NeuroImage* 16, 484–512.
- Friston, K.J., Penny, W., Phillips, C., Kiebel, S., Hinton, G., Ashburner, J., 2002b. Classical and Bayesian inference in neuroimaging: theory. *NeuroImage* 16, 465–483.
- Golinger, J.C., Hughes, E.S.R., 1951. Sensibility of the rectum and colon: its role in the mechanism of anal continence. *Lancet* 1, 543–548.
- Grefkes, C., Eickhoff, S.B., Zilles, K., Fink, G.R., 2005. Differential activation of sensorimotor areas during tactile shape processing: fMRI and cytoarchitecture in humans. *NeuroImage* 26, 23.
- Hobday, D.I., Aziz, Q., Thacker, N., Hollander, I., Jackson, A., Thompson, D.G., 2001. A study of the cortical processing of ano-rectal sensation using functional MRI. *Brain* 124, 361–368.
- Hobson, A.R., Furlong, P.L., Worthen, S.F., Hillebrand, A., Barnes, G.R., Singh, K.D., Aziz, Q., 2005. Real-time imaging of human cortical activity evoked by painful esophageal stimulation. *Gastroenterology* 128, 610–619.
- Holmes, C.J., Hoge, R., Collins, L., Woods, R., Toga, A.W., Evans, A.C., 1998. Enhancement of MR images using registration for signal averaging. *J. Comput. Assist. Tomogr.* 22, 324–333.
- Kaas, J.H., Collins, C.E., 2003. The organization of somatosensory cortex in anthropoid primates. *Adv. Neurol.* 93, 57–67.
- Kell, C.A., von Kriegstein, K., Rösler, A., Kleinschmidt, A., Laufs, H., 2005. The sensory cortical representation of the human penis: revisiting somatotopy in the male homunculus. *J. Neurosci.* 25, 5984–5987.
- Kern, M.K., Shaker, R., 2002. Cerebral cortical registration of subliminal visceral stimulation. *Gastroenterology* 122, 290–298.
- Kern, M.K., Jaradeh, S., Arndorfer, R.C., Jesmanowicz, A., Hyde, J., Shaker, R., 2001. Gender differences in cortical representation of rectal distension in healthy humans. *Am. J. Physiol. Gastrointest. Liver Physiol.* 281, G1512–G1523.
- Kiebel, S., Holmes, A.P., 2003. The general linear model. In: Frackowiak, R.S., Friston, K.J., Frith, C.D., Dolan, R.J., Price, C.J., Ashburner, J., Penny, W.D., Zeki, S. (Eds.), *Human Brain Function*. Academic Press.
- King, A.B., Menon, R.S., Hachinski, V., Cechetto, D.F., 1999. Human forebrain activation by visceral stimuli. *J. Comp. Neurol.* 413, 572–582.
- Krubitzer, L.A., Kaas, J.H., 1990. The organization and connections of somatosensory cortex in marmosets. *J. Neurosci.* 10, 952–974.
- Krubitzer, L.A., Calford, M.B., Schmid, L.M., 1993. Connections of somatosensory cortex in megachiropteran bats: the evolution of cortical fields in mammals. *J. Comp. Neurol.* 327, 473–506.
- Krubitzer, L., Clarey, J., Tweedale, R., Elston, G., Calford, M., 1995. A redefinition of somatosensory areas in the lateral sulcus of macaque monkeys. *J. Neurosci.* 15, 3821–3839.
- Ladabaum, U., Minoshima, S., Owyang, C., 2000. Pathobiology of visceral pain: molecular mechanisms and therapeutic implications: V. Central nervous system processing of somatic and visceral sensory signals. *Am. J. Physiol.: Gastrointest. Liver Physiol.* 279, G1–G6.
- Ladabaum, U., Minoshima, S., Hasler, W.L., Cross, D., Chey, W.D., Owyang, C., 2001. Gastric distention correlates with activation of multiple cortical and subcortical regions. *Gastroenterology* 120, 369–376.
- Langhorst, P., Schulz, B.G., Seller, H., Koepchen, H.P., 1996. Convergence of visceral and somatic afferents on single neurones in the reticular formation of the lower brain stem in dogs. *J. Auton. Nerv. Syst.* 57, 149–157.
- Loening-Baucke, V., Yamada, T., 1993. Cerebral potentials evoked by rectal distention in humans. *Electroencephalogr. Clin. Neurophysiol.* 88, 447–452.
- Loening-Baucke, V., Read, N.W., Yamada, T., Barker, A.T., 1994. Evaluation of the motor and sensory components of the pudendal nerve. *Electroencephalogr. Clin. Neurophysiol.* 93, 35–41.
- Lotze, M., Wietek, B., Birbaumer, N., Ehrhardt, J., Grodd, W., Enck, P., 2001. Cerebral activation during anal and rectal stimulation. *NeuroImage* 14, 1027–1034.
- Mayer, E.A., Berman, S., Suyenobu, B., Labus, J., Mandelkern, M.A., Naliboff, B.D., Chang, L., 2005. Differences in brain responses to visceral pain between patients with irritable bowel syndrome and ulcerative colitis. *Pain* 115, 398–409.
- Naito, E., Roland, P.E., Grefkes, C., Choi, H.J., Eickhoff, S., Geyer, S., Zilles, K., Ehrsson, H.H., 2005. Dominance of the right hemisphere and role of area 2 in human kinesthesia. *J. Neurophysiol.* 93, 1020–1034.
- Naliboff, B.D., Derbyshire, S.W., Munakata, J., Berman, S., Mandelkern, M., Chang, L., Mayer, E.A., 2001. Cerebral activation in patients with irritable bowel syndrome and control subjects during rectosigmoid stimulation. *Psychosom. Med.* 63, 365–375.
- Penny, W.D., Holmes, A.P., 2003. Random effects analysis. In: Frackowiak, R.S., Friston, K.J., Frith, C.D., Dolan, R.J., Price, C.J., Ashburner, J., Penny, W.D., Zeki, S. (Eds.), *Human Brain Function*. Academic Press.
- Qi, H.X., Lyon, D.C., Kaas, J.H., 2002. Cortical and thalamic connections of the parietal ventral somatosensory area in marmoset monkeys (*Callithrix jacchus*). *J. Comp. Neurol.* 443, 168–182.
- Rosen, S.D., Paulesu, E., Frith, C.D., Frackowiak, R.S., Davies, G.J., Jones, T., Camici, P.G., 1994. Central nervous pathways mediating angina pectoris. *Lancet* 344, 147–150.
- Ruben, J., Schwiemann, J., Deuchert, M., Meyer, R., Krause, T., Curio, G., Villringer, K., Kurth, R., Villringer, A., 2001. Somatotopic organization of human secondary somatosensory cortex. *Cereb. Cortex* 11, 463–473.
- Schnitzler, A., Volkmann, J., Enck, P., Frieling, T., Witte, O.W., Freund, H.J., 1999. Different cortical organization of visceral and somatic sensation in humans. *Eur. J. Neurosci.* 11, 305–315.
- Sengupta, J.N., Gebhart, G.F., 1994. Characterization of mechanoreceptive pelvic nerve afferent fibres innervating the colon of the rat. *J. Neurophysiol.* 71, 2060.
- Stephan, E., Pardo, J.V., Faris, P.L., Hartman, B.K., Kim, S.W., Ivanov, E.H., Daughters, R.S., Costello, P.A., Goodale, R.L., 2003. Functional neuroimaging of gastric distention. *J. Gastrointest. Surg.* 7, 740–749.
- Strigo, I.A., Duncan, G.H., Boivin, M., Bushnell, M.C., 2003. Differentiation of visceral and cutaneous pain in the human brain. *J. Neurophysiol.* 89, 3294–3303.
- Strigo, I.A., Albanese, M.C., Bushnell, M.C., Duncan, G.H., 2005. Visceral and cutaneous pain representation in parasyllian cortex. *Neurosci. Lett.* 384, 54–59.
- Vandenbergh, J., Dupont, P., Fischler, B., Bormans, G., Persoons, P., Janssens, J., Tack, J., 2005. Regional brain activation during proximal stomach distention in humans: a positron emission tomography study. *Gastroenterology* 128, 564–573.
- Verne, G.N., Himes, N.C., Robinson, M.E., Gopinath, K.S., Briggs, R.W., Crosson, B., Price, D.D., 2003. Central representation of visceral and

- cutaneous hypersensitivity in the irritable bowel syndrome. *Pain* 103, 99–110.
- Whitehead, W.E., Schuster, M.M., Engel, B.T., 1981. Perception of rectal distension is necessary to prevent fecal incontinence. *Brain and Behaviour*. Akademiai Kiado, Budapest, pp. 203–209.
- Wu, C.W., Kaas, J.H., 2003. Somatosensory cortex of prosimian Galagos: physiological recording, cytoarchitecture, and corticocortical connections of anterior parietal cortex and cortex of the lateral sulcus. *J. Comp. Neurol.* 457, 263–292.
- Yaguez, L., Coen, S., Gregory, L.J., Amaro Jr., E., Altman, C., Brammer, M.J., Bullmore, E.T., Williams, S.C., Aziz, Q., 2005. Brain response to visceral aversive conditioning: a functional magnetic resonance imaging study. *Gastroenterology* 128, 1819–1829.
- Young, J.P., Herath, P., Eickhoff, S., Choi, J., Grefkes, C., Zilles, K., Roland, P.E., 2004. Somatotopy and attentional modulation of the human parietal and opercular regions. *J. Neurosci.* 24, 5391–5399.
- Zilles, K., Eickhoff, S., Palomero-Gallagher, N., 2003. The human parietal cortex: a novel approach to its architectonic mapping. *Adv. Neurol.* 93, 1–21.