Effects of Attention on Visceral Stimulus Intensity Encoding in the Male Human Brain

STEVEN J. COEN,* QASIM AZIZ,* LIDIA YÁGÜEZ,† MICK BRAMMER,‡ STEVEN C. R. WILLIAMS,‡ and LLOYD J. GREGORY†

*Wingate Institute for Neurogastroenterology, Queen Mary University of London, London; †Neuroimaging Research Group, Institute of Psychiatry, King’s College, London; ‡Department of Psychology, Institute of Psychiatry, King’s College, London; and †R&D Directorate, Salford Royal NHS Foundation Trust, Salford, United Kingdom

Background & Aims: Hypervigilance is considered important in pain perception in functional gastrointestinal disorders. Nonetheless, a comprehensive assessment of the influence of attention on brain processing of visceral sensation has not been performed. We investigated the effects of attention on esophageal pain perception and brain activity.

Methods: Twelve healthy male volunteers (age range, 21–32 years) underwent 4 functional magnetic resonance imaging scans incorporating 4 levels of esophageal stimulation (ES), ranging from nonpainful to painful, during which they completed a task aimed at distracting them from the esophageal stimulus. The volunteers were then scanned a fifth time, during painful stimulation without distraction.

Results: Following ES during distraction, there was a significant linear trend (P < .05) in which the intensity of cerebral activation in the primary somatosensory cortex (SI) (bilateral) and left mid-anterior cingulate cortex (ACC) increased with stimulation intensity. When pain was delivered during distraction, there was a significant reduction in pain ratings, accompanied by significant decreases (P < .05) in brain activity in the right ACC and right prefrontal cortex. There was no effect of distraction on SI activity (P < .05).

Conclusions: Our results suggest that the SI is involved in processing sensory-discriminative aspects of visceral sensation. In contrast, activity in the mid-ACC suggests that this region is multifunctional because it appears to be involved in sensory and cognitive appraisal of visceral pain; the right prefrontal cortex seems to be involved in only cognitive responses to pain.

In purely physiologic terms, perceived pain correlates well with intensity of noxious input. However, pain perception can be influenced by many factors. In particular, psychologic factors such as stress, anxiety, mood, and personality1–4 and cognitive phenomena such as learning, anticipation, attention/distraction, and the placebo effect have been shown to influence the pain experience.5–10 Perhaps the most thoroughly studied area of cognition and pain is the role of attention, modulation of which has been shown to alter perception of pain.11,12 These studies demonstrate that volunteers report lower pain scores when distracted from the painful stimulus; in contrast, when individuals focus their attention toward the painful stimulus, they report higher pain scores.11–13

There have been relatively few studies investigating the role of attention in modulating the brain processing of visceral pain. Previous work from our laboratory has involved the use of nonpainful esophageal stimulation and visual stimuli during a selective/divided attention task.7 Selectively attending to esophageal or visual stimulation activated the relevant modality-specific neural network. However, when attention was divided between the visual and esophageal stimuli, more neural resources were devoted to the visceral stimuli, providing neurobiologic evidence of the salience of sensations arising from the viscera. This study used a nonpain esophageal stimulus, which means that the effect of attentional modulation on the brain processing of visceral pain has yet to be explored.

More recently, work from our group has established that there is a correlation between the intensity of esophageal stimulation and intensity of brain activation in the mid-anterior cingulate cortex (ACC) and the somatosensory cortex (SI).14 Despite current knowledge about the functional role of these regions, it is still unclear as to the meaning of this relationship. There is much evidence to suggest that the ACC is involved in attentional and emotional aspects of pain processing; conversely, there is also a body of evidence that suggests a role for the ACC in encoding the sensory discriminative aspects of pain processing.15,16 Typically, the primary SI is believed to play an important role in sensory-discriminative aspects of pain,17,18 including encoding of the intensity of sen-

Abbreviations used in this paper: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; PT, pain threshold; SI, somatosensory cortex; ST, sensory threshold.

© 2008 by the AGA Institute
0016-5085/08/$34.00
doi:10.1053/j.gastro.2008.08.005
sory information.\textsuperscript{11,19,20} However, the SI has also been implicated in cognitive-motivational mechanisms, such as attention.\textsuperscript{11}

Therefore, the purpose of this study was to examine the possible contribution of attention to the dose-dependent brain response to visceral stimulation particularly in the ACC and SI to clarify the functional roles of these 2 neuroanatomic locations. Using a distraction task, our aim was 2-fold: (1) to determine whether the intensity response relationship to esophageal stimulation was still present in the SI and the ACC when attention was controlled and (2) to investigate the effects of distraction on the brain processing of visceral pain.

\section*{Materials and Methods}

\subsection*{Subjects}

Twelve healthy volunteers (all male; mean age, 26 years; range 21–32 years) participated in the study. Given that we wanted to study a homogenous group, we decided to recruit only males in our study because previous findings suggest the possibility of sex differences in cortical response following visceral stimulation.\textsuperscript{21} All subjects gave informed written consent prior to intubation and scanning. The study was approved by the local Ethics Committee for research (Institute of Psychiatry Ethical Committee reference 311/03).

\subsection*{Esophageal Stimulation}

A standard manometry catheter (3-mm-diameter tube) to which a 2-cm-long silicone balloon was attached was passed transnasally into the distal smooth muscle section of the esophagus (positioned 35 cm from the nostril, roughly 5–7 cm from the lower esophageal sphincter). The catheter was connected to a magnetic resonance imaging (MRI) compatible, purpose built pump (Medical Physics Department; Hope Hospital, Salford, United Kingdom), capable of rapidly distending the balloon to varying intensities (maximum flow rate 200 mL/second, rise time to maximum balloon inflation 165 ms for any given pressure, range 0 to 35 psi). The pressure of the air used to inflate the balloon was varied to produce 4 quantifiable intensities of esophageal sensation. Each level was achieved quantitatively by obtaining a percentage of the difference in balloon pressure between sensory threshold (ST) and pain threshold (PT) as described by Hobson et al.\textsuperscript{22} In brief, ST was quantified as 0% and PT as 100%. Both PT and ST were measured 3 times for each volunteer and thresholds set as the mean of the 3 recordings. Stimulation was then performed at pressures representing 25%, 50%, 75%, and 100% of the difference between ST and PT. To avoid any disturbance of the position of the balloon, thresholding was performed while the volunteer was lying supine on the functional MRI (fMRI) scanning table immediately prior to scanning acquisition.

\subsection*{Study Design: Distraction Task}

A distraction task known as “1-back” was used and was chosen based on pilot data. The 1-back task has been used in a number of previous fMRI experiments to study working memory and cognitive control.\textsuperscript{23} We used a letter version, involving sequential presentation of letters, which puts a constant demand on attentional resources by requiring permanent update and retrieval of relevant pieces of information as volunteers attend to the presentation of each letter and respond to any letter identical to the one preceding it (ie, 1 letter back) (see Figure 1). Volunteers respond by pressing a button, using their right index finger on a handheld response box connected to a PC. The PC then stores responses so that response times and accuracy can be calculated.

In this study, letters were presented in a pseudorandomized sequence centrally on a screen using a projector. Each letter was presented on screen for 1.5 seconds, with an interstimulus interval of 0.5 seconds. The stimuli were presented in 10 blocks of 15 letters (30 seconds per block) separated by a 6-second interval during which a visual analogue scale (VAS) was used to measure intensity of esophageal stimulation on a 10-point scale (0, no sensation; 5, discomfort; 10, worst imaginable pain). The time taken to complete a run was 6 minutes.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Pictorial representation of the 1-back task. Volunteers see a sequence of letters on a computer screen and have to respond by pressing a button every time a letter identical to the one preceding it (1-back) appears.}
\end{figure}
**MRI Protocol**

Volunteers attended 1 session with the following protocol: 4 separate block design functional imaging experiments, each incorporating 1 of 4 intensities (25%, 50%, 75%, and 100%). During each experiment, a 30-second block of stimulation was followed by a 30-second block control period during which there was no stimulation. This sequence was repeated 5 times and constituted 1 experimental “run” (see Supplementary Figure 1 online at www.gastrojournal.org for schema detailing the experimental design). Volunteers were blinded to the intensity of the stimulation to avoid any potential confounding effects of anticipation. Throughout the duration of each run (during both on and off blocks), subjects also completed the 1-back task. Response times were measured by pressing a button on a dedicated magnetic resonance (MR) compatible response box. A VAS was used after each block to measure the subjective perception of the stimulus (0, no sensation; 5, discomfort; 10, extreme pain).

An additional fifth experimental run was incorporated into the protocol in which volunteers received painful esophageal stimulation (100% intensity) following the 1-back task. Instead, subjects were instructed to fix their gaze on a cross presented on the projection screen to control for the visual stimulus present during the 1-back. The order in which each level of stimulation was presented was randomized across subjects to avoid any order effects.

**fMRI**

fMRI was performed using a GE Signa 1.5T Neuro-optimized MR system (General Electric, Milwaukee, WI) based at the Eric Buyers Magnetic Resonance Imaging Suite, Maudsley Hospital, London. A quadrature birdcage head coil was used for radio frequency transmission and reception. Head movement was restricted to a minimum by the use of foam padding within the head coil. While inside the scanner, subjects could view a screen on which the 1-back task and electronic version of a VAS were projected. A purpose built button box was placed in the right hand of each subject to allow intensity of esophageal stimulus to be rated and 1-back task to be completed.

**Structural Acquisition**

A gradient echo structural scan for subsequent coregistration (43 × 3-mm slices; 0.3 interslice gap; echo time, 40 ms; repetition time, 3000 ms; flip angle, 90°; matrix, 128; field of view, 240 mm; voxel size, 1.875 × 1.875 mm) was acquired for each volunteer before the experiment commenced.

**Functional Acquisition**

A total of 122 T2* weighted images per slice (16 × 7-mm slices; 0.7 interslice gap; echo time, 40 ms; repetition time, 3000 ms; flip angle, 90°; matrix, 64; field of view, 240 mm; voxel size, 3.75 × 3.75 mm), depicting BOLD contrast, was collected over a 6-minute and 6-second period of continuous acquisition, during each experimental run.

**Generic Brain Activation Mapping**

All MRI data were processed using in-house software XBAM (http://brainmap.co.uk/). For information on fMRI data preprocessing, smoothing, and individual brain activation mapping methods, please see Supplementary Material (see Supplementary material online at www.gastrojournal.org).

**Analysis of Variance**

To compare responses between runs (for example, pain alone vs pain during distraction), an analysis of variance (ANOVA) model was fitted to the sum of squares quotient (SSQ) data (where SSQ ratio) at each intracerebral voxel as follows: $\beta_0 + \beta_1 G + e$, where $\beta_0$ is the intercept, $\beta_1$ the size of the intersession difference in response, $G$, the element of the contrast matrix $G$ for individual $i$ (eg, $-1$ or 1), and $e$, the residual error after model fitting for individual $i$.

The null hypothesis was tested by comparing coefficient $\beta_1$ to critical values of its nonparametrically obtained null distribution. Critical values for a 2-tailed test of size $\alpha$ ($\alpha$ can be any desired type I error rate for the test) are the 100*(1-$\alpha/2$)th and 100*(1+$\alpha/2$)th percentile values of this distribution. This ANOVA model delineates the between-group differences in brain activation maps with the significance level of $P = .01$ or better. Once regions had been identified on the ANOVA, data (average SSQ ratio values) were extracted from these regions and tested for significance up to $P < .05$ using repeated measures analyses of variance and post hoc matched-pairs $t$ tests. All tests were corrected for multiple comparisons.

**Trend Analysis**

In addition to this, the ANOVA was used to investigate the data further by linear and quadratic trend analysis. Maps of the ratios of the model to residual sum of squares (SSQ ratio) were calculated for each of the 5 experimental runs for each individual and transformed into standard space. These standard space maps were then analyzed by fitting orthogonal linear and quadratic trends at each voxel (orthogonal polynomial trend analysis). To find the direction of the trend, a standardized power of response (SSQ) for each subject was extracted from each cluster showing a trend and plotted on a graph showing level of stimulation on the x-axis and SSQ value on the y-axis. As with our previous papers (eg, Coen et al13)), the trend analysis on these data was of the whole curve rather than all possible pair-wise comparisons (which would need a multiple comparison correction).
However, to investigate the data in more detail, we also conducted post hoc multiple comparison tests on the SSQs in each region showing a significant trend. All tests were corrected for multiple comparisons.

**Behavioral Data**

Data were tested for differences and effect of intensity of stimulation on VAS ratings using a nonparametric Friedman test and post hoc Wilcoxon signed-ranks test. Mean reaction times corresponding to the 1-back task were analyzed using repeated measures ANOVA and Turkey multiple comparison post hoc test.

**Results**

**Behavioral Data**

All subjects tolerated the study well. There was a significant increase in balloon pressure required to reach PT compared with ST (mean balloon pressure [psi] PT = 16.5 ± 1.3, ST = 9.2 ± 0.9 Z = 3.06, P < .02). Mean VAS scores increased significantly with rising stimulation intensities (Friedman statistic = 35.5, P = .001) (see Figure 2A). Perception of the stimulus was significantly greater for each condition as the intensity of esophageal stimulation increased (P < .05). Furthermore, there was a significant increase in perceived intensity of esophageal stimulation when painful stimulation was presented alone compared with painful stimulation during distraction (P < .05).

**1-Back Response**

Mean response times and accuracy of response were calculated and are summarized in Figure 2B. There was no effect of stimulation intensity on mean response time (P > .05). Group mean percentage accuracy of response was calculated for each intensity of stimulation. The data summarized show no significant effect of pain on performance of the 1-back task (P > .05) (see Figure 2C for a summary).

**Group Brain Activation**

Activation following the 4 levels of stimulation was consistent with our previous study, which identified a robust visceroneuromatrix. Regions activated included the SI, secondary somatosensory cortex, insula, superior temporal gyrus, supplementary motor area, dorsolateral prefrontal cortex (DLPFC), and inferior frontal gyrus. To avoid repetition, the brain activation data have been summarized in 2 tables representing (1) nonpainful (50% combined with distraction) and (2) painful (100% with distraction) (see Tables 1 and 2). Finally, a summary of major brain regions activated following painful stimulation without distraction is also listed in Table 3. Critically, the 2 brain regions that are the focus of this study, the SI and mid-ACC, were also activated. The results for these regions are summarized below.

![Figure 2](image-url)

**Figure 2.** (A) Median group pain ratings with 25% and 75% percentiles (±SEM) for each intensity of esophageal stimulation during distraction and painful stimulation alone. Perceived pain intensity increased significantly (P = .001) with higher stimulation levels. Analysis also showed a significant increase in perceived intensity of esophageal stimulation when painful stimulation was presented alone, compared with painful stimulation during distraction (P < .05). (B) Mean group response times to 1-back task during 4 levels of esophageal stimulation. There was no significant difference in response times between varying levels of esophageal stimulation. (C) Mean percentage accuracy (+SEM) on 1-back task for each condition. As can be seen by studying the Figure, there is no significant difference in response times between conditions (P > .05).
Table 1. Summary of Major Brain Regions Activated by Nonpainful Esophageal Stimulation

<table>
<thead>
<tr>
<th>Size</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Side</th>
<th>Cerebral region</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>54</td>
<td>4</td>
<td>4</td>
<td>R</td>
<td>Superior temporal gyrus</td>
</tr>
<tr>
<td>27</td>
<td>54</td>
<td>4</td>
<td>9</td>
<td>R</td>
<td>Precentral gyrus (motor cortex)</td>
</tr>
<tr>
<td>25</td>
<td>−4</td>
<td>30</td>
<td>42</td>
<td>L</td>
<td>Medial frontal gyrus (SMA BA6)</td>
</tr>
<tr>
<td>24</td>
<td>43</td>
<td>15</td>
<td>31</td>
<td>R</td>
<td>Middle frontal gyrus (DLPC BA9/46)</td>
</tr>
<tr>
<td>17</td>
<td>−54</td>
<td>7</td>
<td>4</td>
<td>L</td>
<td>Superior temporal gyrus</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>19</td>
<td>42</td>
<td>R</td>
<td>Anterior cingulate gyrus (BA32)</td>
</tr>
<tr>
<td>13</td>
<td>−58</td>
<td>−15</td>
<td>15</td>
<td>L</td>
<td>Postcentral gyrus (SI)</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>−4</td>
<td>9</td>
<td>R</td>
<td>Postcentral gyrus (SI)</td>
</tr>
<tr>
<td>10</td>
<td>47</td>
<td>19</td>
<td>37</td>
<td>R</td>
<td>Middle frontal gyrus (DLPC BA9)</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>19</td>
<td>26</td>
<td>R</td>
<td>Anterior cingulate gyrus (BA24)</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>15</td>
<td>4</td>
<td>R</td>
<td>Insula</td>
</tr>
</tbody>
</table>

NOTE. Nonpainful esophageal stimulation is 50% intensity. Talairach and Tournoux coordinates in millimeters (x, y, z); side, left (L), right (R); BA, Brodmann area, size = number of voxels. The coordinates for each cluster represent points of maximum activation at the group level (highest median response in the cluster). Clusters defined using cluster mass statistics and therefore do not have cluster size limitations.

Primary Somatosensory Cortex

A trend analysis revealed a significant trend ($P < .05$) in intensity of cerebral activation bilaterally in SI, which increased with rising stimulation levels (see Figure 3). Multiple comparison tests revealed significant differences between 25% vs 100% intensity ($P < .05$) in the left SI and 25% vs 100% ($P < .02$) and 75% vs 100% ($P < .04$) in the right SI.

Table 2. Summary of Major Brain Regions Activated by Painful Esophageal Stimulation

<table>
<thead>
<tr>
<th>Size</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Side</th>
<th>Cerebral region</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>−54</td>
<td>−4</td>
<td>15</td>
<td>L</td>
<td>Postcentral gyrus (SI):</td>
</tr>
<tr>
<td>46</td>
<td>47</td>
<td>4</td>
<td>4</td>
<td>R</td>
<td>Insula</td>
</tr>
<tr>
<td>37</td>
<td>58</td>
<td>−16</td>
<td>13</td>
<td>R</td>
<td>Postcentral gyrus (SI):</td>
</tr>
<tr>
<td>37</td>
<td>−51</td>
<td>−4</td>
<td>4</td>
<td>L</td>
<td>Superior temporal gyrus</td>
</tr>
<tr>
<td>32</td>
<td>54</td>
<td>−4</td>
<td>9</td>
<td>R</td>
<td>Precentral gyrus</td>
</tr>
<tr>
<td>27</td>
<td>−4</td>
<td>7</td>
<td>42</td>
<td>L</td>
<td>Cingulate gyrus (BA24)</td>
</tr>
<tr>
<td>24</td>
<td>54</td>
<td>0</td>
<td>2</td>
<td>R</td>
<td>Superior temporal gyrus</td>
</tr>
<tr>
<td>23</td>
<td>7</td>
<td>26</td>
<td>31</td>
<td>R</td>
<td>Cingulate gyrus (BA32)</td>
</tr>
<tr>
<td>19</td>
<td>60</td>
<td>−34</td>
<td>20</td>
<td>R</td>
<td>Secondary somatosensory cortex (SII)</td>
</tr>
<tr>
<td>15</td>
<td>−29</td>
<td>−4</td>
<td>48</td>
<td>L</td>
<td>Middle frontal gyrus (DLPC)</td>
</tr>
<tr>
<td>15</td>
<td>43</td>
<td>30</td>
<td>26</td>
<td>R</td>
<td>Middle frontal gyrus (BA46/9)</td>
</tr>
<tr>
<td>3</td>
<td>−36</td>
<td>4</td>
<td>15</td>
<td>L</td>
<td>Insula</td>
</tr>
</tbody>
</table>

NOTE. Painful esophageal stimulation is 100% intensity. Talairach and Tournoux coordinates in millimeters (x, y, z); side, left (L), right (R); BA, Brodmann area, size = number of voxels. The coordinates for each cluster represent points of maximum activation at the group level (highest median response in the cluster). Clusters defined using cluster mass statistics and therefore do not have cluster size limitations.

Mid-Anterior Cingulate Cortex

The same trend analysis also highlighted a significant effect of stimulation level on intensity of brain activation in the left mid-ACC (see Figure 3 for more detail on the dose response relationship seen in the ACC). A multiple comparison test revealed significant differences between 25% vs 100% intensity ($P < .03$) and 75% vs 100% ($P < .05$).

Figure 3. This figure shows the relationship between intensity of brain activity (SSQ, ±SEM) and esophageal stimulation intensity in the SI and ACC. As can be seen, intensity of activation increases with rising stimulation levels in bilateral SI and left ACC from nonpainful (25%) to (100%) painful stimulation. This relationship was found to be significant whereby brain activation increased with rising stimulation levels ($P = .05$).
Pain + Distraction vs Pain Alone

An ANOVA between pain plus distraction and pain without distraction highlighted a significantly ($P < .05$) lower right mid-ACC (BA24) activity when attention was distracted from the esophageal stimulus (Figure 4). When activity in SI was compared between pain distraction and pain alone, there was no significant difference in brain activity in this region.

Further comparisons between pain + distraction and pain alone were carried out to see whether there was an effect of distraction on brain regions other than SI and mid-ACC. Activity in both the superior frontal gyrus (BA10) and DLPFC (BA9) was significantly ($P < .05$) less during the distraction condition ($P < .05$). Other regions of the frontal cortex that showed a similar modulation ($P < .05$) included 3 regions within the middle frontal gyrus (BA44, BA46, and BA47). All significant differences between pain + distraction and pain alone were localized to the right hemisphere. An example of these interactions is shown below for the DLPFC and superior frontal gyrus (see Figures 4 and 5 for a summary).

Discussion

The primary aim of this study was to investigate the role of attention in the relationship between intensity of esophageal stimulation and brain activation. To this end, we used an attentionally demanding task to investigate the effects of distraction on pain perception and related brain activity compared with pain delivered without distraction. The results show that a linear relationship between intensity of brain activity and stimulation level exists bilaterally in the SI when attention is controlled but only unilaterally to the left mid-ACC. We also demonstrate a decrease in activity in the right mid-ACC and frontal cortex when attention is distracted from esophageal pain compared with pain presented alone.

Behavioral Data

The data show that pain perception increased with rising stimulation levels. These data also demonstrate that mean reaction times were not affected by the intensity of esophageal stimulation. This suggests that the distraction task was engaging enough to avoid the potential for more intense painful stimuli to interfere with the task. In addition, accuracy on the task was highly consistent across all stimulation intensities.

Perhaps the most interesting behavioral result in this study was the significant increase in pain perception when the distraction task was not present. This result suggests that attention modulates pain perception, a finding noted in many studies of somatic pain in the past.9,11–13,27

Brain Activity

It is well-known that distracting attention from pain results in lowered pain perception11–13,31; however, the neural basis for this in the processing of visceral pain has remained vague. Our results suggest that certain brain regions show a significant modulation in activity when pain with and without distraction are compared, as well as showing an effect of distraction on the intensity-dependent relationship in the right ACC.

Mid-Anterior Cingulate Cortex

Previous work from our group14 has identified a relationship between level of esophageal stimulation and intensity of brain activity in the left and right ACC. However, determining the functional nature of this relationship was complex because of the mid-ACC previously being implicated in attentional, sensory, and affective processing of pain.6,28,29 In the present study, the same levels of stimulation as previously described14 were applied to each volunteer, except, on this occasion, the level of attention was controlled to assess the influence of attention on the dose-dependent relationship seen in the ACC. The results show an increase in brain activity with rising stimulation level in the left ACC as seen in our previous study.14 However, the data also show that, when attention is controlled, there is no intensity encoding in the right ACC. Furthermore, a comparison between brain activity during pain + distraction and pain alone revealed an increase in brain activity in the right mid-ACC when pain was delivered alone. There was no significant effect of distraction on left ACC activity. Therefore, whereas the data do not show any significant effect of attentional modulation on the left ACC (as this still appears to encode for intensity), there is the suggestion of the possibility of a cognitive rather than stimulus intensity-dependent relationship in the right ACC. Indeed, it may be that the correlation between level of
stimulation intensity and right ACC activity observed in our previous study was not a result of sensory encoding of stimulus intensity but rather a result of increasing attention devoted toward the balloon inflation as it became more painful and more salient, which does not occur in the present study when attention is controlled.

The suggestion of ACC involvement in processing attentional aspects of pain is not entirely surprising because modulation of mid-ACC activity has been reported in previous imaging studies involving somatic pain and cognitive modulation.29–31 What is surprising is the apparent division between the left ACC and the right ACC because it seems that the right ACC in particular is modulated by attention. The reason for this is not entirely certain, although, when data from the prefrontal cortex are considered, there is striking evidence of laterality of neural activity to the right side of the brain when pain is delivered without distraction compared with pain during distraction. The reason for such a division between right and left hemisphere is unclear, but studies of somatic pain have suggested a possible preferential role of the right hemisphere in attributing emotional valance to the negative component of a painful experience.32

Further studies, involving emotional manipulation, have also shown evidence of a division for the processing of positive (left hemisphere) and negative affect (right hemisphere). Such observations have led to a general theory suggesting a neuroanatomic basis for functional asymmetry proposing that the left hemisphere is associated with predominantly parasympathetic activity (such as nourishment, safety, positive affect) and the right hemisphere with sympathetic activity (such as arousal, danger, withdrawal behavior, and negative affect).33 In particular, Craig suggests that the right ACC interacts primarily with the right insula and together both regions are integral for subjective awareness of emotion.33 Moreover, Craig’s suggestion that the right anterior insula and right ACC provide a neurobiologic substrate for subjec-

Figure 5. Group activation map showing brain regions in which there was significantly (P = .05) increased activity during painful stimulation alone compared with pain during distraction. Activity was found to be significantly more intense in (A) BA10 of the right frontal gyrus, (B) the right ACC (BA24), (C) BA44 of the right frontal gyrus, and (D) right frontal gyrus (BA47) when attention was not distracted from the painful esophageal stimulus.
tive awareness of emotion (lateralized to the right hemisphere) is consistent with the James–Lange theory of emotion and Damasio’s somatic marker hypothesis. Therefore, whereas it may be speculative to propose, the results of the current study could suggest that the right ACC is more active during pain alone for 2 possible reasons: (1) because of an increase in unpleasantness of the experience when attention is not distracted and, also (in tandem), (2) when volunteers are not distracted, they become more subjectively aware of the painful stimulus resulting in an increase in right ACC activity.

Primary Somatosensory Cortex

This study highlights an intensity-dependent bilateral response in the SI. The reason for studying this interaction further was in an attempt to interrogate the functional nature of this relationship. Our results show that SI activity increases with visceral afferent input despite attention being kept constant. Previous studies heavily support the view that the SI is involved in sensory aspects of pain processing. In fact, several studies using noxious heat stimulation and pain-evoked single unit activity in monkeys have shown that, whereas cognitive modulation of pain influences nociceptive activity in the medullary dorsal horn and in the medial thalamus, there is little or no modulation of the ventro-posterior thalamus, which is thought to mediate somatosensory responses to pain. This has led to the suggestion that modulation of pain through cognitive manipulation may take place in regions previously shown to be involved in pain affect, in particular via the medial thalamic pathway to the ACC and not the somatosensory pathway.

However, it should be noted that some studies have shown an effect of attentional modulation on SI activity in humans. The reason SI activity is modulated by attention in previous studies involving somatic pain but not during visceral pain is uncertain. However, many of the studies that have shown an effect of attention on SI activity involve tasks that specifically require volunteers to focus their attention on the location and sensory characteristics of the stimulus such as intensity and unpleasantness. Had we asked volunteers to perform a similar task, we may have seen an effect of attention on SI activity, as such a task inherently involves more sensory discriminative processing.

Trend Analysis

One interesting observation of the trend analysis is that the increase in brain activity from 75% to 100% is larger and more steep compared with the increments from 25% to 50% and 50% to 75%. This observation is particularly interesting because it is consistent across all 3 brain areas (left ACC and bilateral SI [statistically significant for left ACC and right SI]). The exact reason for this is unclear; however, one explanation could be that, between 75% and 100%, the sensation goes from being nonpainful to painful. This is arguably a unique step compared with all other increments as additional factors specific to pain such as cognition-evaluative and affective-motivational processes become important. These additional components could certainly account for an increase in brain activity in the ACC and possibly the SI. In addition, the painful stimulus would lead to specific activation of nociceptive fibers, which could result in additional brain activity in the SI bilaterally.

Frontal Cortex

In addition to observations seen in the ACC and SI, an effect of distraction was also seen in the right frontal cortex where brain activity increased when pain was delivered alone compared with pain with distraction. Previous studies have shown the right frontal cortex to be more active in males and the left venrolaterprefrontal cortex being more active in females following visceral stimulation, and there have been several previous studies showing lateralization of prefrontal cortex activity to the right hemisphere during attentional-related activity. More importantly, this finding is interesting because several previous studies involving visceral pain have identified the right venrolaterprefrontal cortex as being involved in corticollimbic inhibition of pain. The suggestion that the right prefrontal cortex is involved in corticollimbic inhibition is supported further by the fact that there is a well characterized, if not fully understood, opiate-sensitive descending pathway that descends from the frontal cortex to the amygdala, periaqueductal grey, rostral ventral medulla, and onto the spinal dorsal horn. In contrast to the present study, the findings by Fields and Villemure and Bushnell show that increased activity in the frontal cortex is associated with a decrease in pain sensation rather than an increase as seen in the current data. The findings by Fields and Villemure and Bushnell are supported further by Kong et al, who concluded that cognitive processes such as the placebo effect are associated with increased activity of the DLPFC and a decrease in pain ratings. Whereas our results contradict previous data, the present findings could suggest that the right prefrontal cortex is involved in both inhibition and excitation of the proposed opiate-sensitive descending pathway and that, in this case, an increase in brain activity during pain alone is because of increased attention and inhibition of the opiate-sensitive descending pathway. Although the impact of attentional modulation on this pathway is not fully understood, other regions such as the periaqueductal grey have been shown to be modulated by cognitive manipulation resulting in reduced pain scores, suggesting that this pathway can influence top-down mechanisms such as attention. The present study provides evidence supportive of the fact that there is a modulatory effect of attention on this region resulting in reduced pain perception scores.
Interaction Between Pain Perception and ACC, SI, and Frontal Cortex

Perhaps one of the most common and robust observations in pain and functional brain imaging research is the correlation between perceived perception of pain and brain activity in SI. However, the current study shows no change in SI activity despite a significant reduction in pain perception ratings during distraction from pain. We also provide compelling evidence to suggest that there is a relationship between SI activity and stimulation level when attention is controlled. This observation suggests that the analgesic effect of distraction is a cognitive phenomena that does not involve inhibition of primary afferent responses but more top-down modulation of cognitions via the ACC and frontal cortex, resulting in an altered interpretation of sensory information. If this is indeed the case, this observation may explain the usefulness of interventions such as cognitive behavior therapy in patients with unexplained visceral pain symptoms such as patients with irritable bowel syndrome.

Limitations

We only recruited males to our sample, and, as such, it is not clear to what extent sex may be important in the modulation of brain responses to visceral pain by attention. In relation to this, the effects of lateralization of brain activity as seen in this study must be approached with caution because it is possible that this may be a sex effect. However, it is important to note that, although sex differences in cortical activation following visceral stimulation have been shown, the evidence is not conclusive, and an agreement on this subject has yet to be achieved. Further research is required to clarify this issue.

The limitations of collecting psychophysic data during fMRI scanning imposed by the nature of the MRI environment means that it was not feasible to explore the possibility of temporal summation or wind-up occurring because of repeated esophageal stimulation. However, recent data suggest that, whereas wind-up in the esophagus occurs at a stimulation frequency of 2 Hz, a frequency of 0.1 Hz does not alter perceptual responses to esophageal stimulation. Furthermore, in the study by Sarkar et al., a train of 20 stimuli was required to achieve wind-up along with a direct electrical stimulus. To avoid sensitization in the current study, we used a frequency of 0.3 Hz and trains of 10 stimuli with 30 seconds of rest between each train. In addition to this, we introduced a 5-minute rest between each run of 50 stimuli and randomized the order of stimuli between volunteers to avoid any potential confounding effects of the most intense stimulation level.

The current investigation was a single session study assessing within-session effects of attentional modulation on brain activity following esophageal stimulation, and, therefore, it was not necessary to assess reproducibility. However, given recent findings suggesting possible habituation of brain activity and perceptual responses over time, future studies investigating attentional modulation over several sessions should account for the effects of serial scanning on any observed brain responses.

Summary and Conclusions

The results of this study help clarify the relationship between intensity of esophageal stimulation and activity in the ACC and SI. The SI appears to be involved in processing sensory-discriminative aspects of pain and does not appear to mediate attention. Based on the results of this study, it might be possible to conclude that the right mid-ACC is involved in attentional aspects of pain processing, whereas the left ACC encodes sensory components. However, it is perhaps more likely that the mid-ACC is a multifunctional region and that precise functional divisions of the mid-ACC may require region of interest imaging studies specifically designed to increase spatial resolution within the ACC and enable precise localization of functional activity within this particular region. The results of this study also highlight the potential for distraction in attenuating visceral pain and altering brain activity. Such alterations may have implications for future studies involving healthy volunteers and patients such that investigators may need to consider controlling for attention when conducting functional brain imaging experiments.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2008.08.005.

References


Supplementary Material

Generic Brain Activation Mapping

Data were processed to remove low-frequency signal changes and minimize the effect of motion-related artefacts. The data were then smoothed using a 7.2-mm FWHM Gaussian filter to improve local signal to noise ratio. The responses at each voxel were analyzed by regressing the corrected time-series data on a linear model produced by convolving each contrast vector with 2 Poisson functions parameterising hemodynamic delays of 4 and 8 seconds. Following least squares fitting of this model, a goodness of fit statistic composed of the ratio of the model to residual sum of squares (sum of squares quotient; SSQ) was calculated (SSQ ratio) for each contrast. The distribution of the same statistics under the null hypothesis of no experimental effect was then calculated by wavelet-based resampling of the time-series at each voxel and refitting the models to the resampled data. An experimentally derived null distribution of the goodness of fit statistic was then derived by following this procedure 10 times at each intracerebral voxel and combining the resulting data. This method has been shown to give excellent control of nominal type I error rates in functional magnetic resonance imaging data from a variety of scanners. Activations for any contrast at any required $P$ value can then be determined by obtaining the appropriate critical values from the null distribution. Generic group activation maps were constructed by mapping the observed and randomized test statistics for each individual into the standard stereotactic space of Talairach and Tournoux and computing and testing median activation maps as previously described.

References