Characterization of the cerebral cortical representation of heartburn in GERD patients

Mark Kern, Candy Hofmann, James Hyde, and Reza Shaker
Medical College of Wisconsin Dysphagia Institute, Division of Gastroenterology and Hepatology, Digestive Disease Center, Biophysics Institute, Medical College of Wisconsin, and Zablocki, Veterans Affairs Medical Center, Milwaukee, Wisconsin 53226

Submitted 21 April 2003; accepted in final form 18 August 2003

Kern, Mark, Candy Hofmann, James Hyde, and Reza Shaker. Characterization of the cerebral cortical representation of heartburn in GERD patients. Am J Physiol Gastrointest Liver Physiol 286: G174–G181, 2004. First published September 25, 2003; 10.1152/ajpgi.00184.2003.—Although symptoms arising from the esophagus such as heartburn and pain can at times become challenging clinical problems, esophageal viscerosensation, especially with regard to chemical stimulation in humans, is incompletely understood. Our aims were 1) to characterize and ascertain the reproducibility of cerebral cortical registration of heartburn and 2) to elucidate the differences between these findings and those of esophageal subliminal acid stimulation in asymptomatic controls. We studied 11 gastroesophageal reflux disease (GERD) patients (9 males, 30–55 yr) and 15 healthy controls (8 males, 21–49 yr). Cerebral cortical functional magnetic resonance imaging (fMRI) activity was recorded twice in each subject, during two 5-min intervals of 0.1 N HCl, separated by 5 min of NaCl perfusion. Time from onset of acid perfusion to instant of fMRI signal increase and first report of heartburn averaged 1.60 ± 0.80 and 1.85 ± 0.60 min, respectively. Average maximum percent signal increase in the GERD patients (16.3 ± 3.5%) was significantly greater than that of healthy controls (3.8 ± 0.9%; P < 0.01). Temporal fMRI signal characteristics during heartburn were significantly different from those of subliminal acid stimulation in controls (P < 0.01). Activated cortical regions included sensory/motor, parieto-occipital, cingulate and prefrontal regions, and the insula. There was 92% concordance between the activated Brodmann areas in repeated studies of GERD patients. Cortical activity associated with perceived and unperceived esophageal acid exposure in GERD patients and healthy controls, respectively, involves multiple brain regions but occurs more rapidly and with greater intensity in GERD patients than the activity in response to subliminal acid exposure in healthy controls. The cortical pain-processing pathway seems to be involved in perception of esophageal acid exposure and could explain the variations encountered in clinical practice defining this sensation.

esophagus; reflux; brain; gastroesophageal reflux disease

HEARTBURN, THE CARDINAL SYMPTOM of gastroesophageal reflux disease (GERD), is a common complaint affecting 7–10% of the U.S. population daily (32, 44) and may develop in the presence or absence of gross esophageal mucosal injury. In ambulatory esophageal pH-monitoring studies, however, only a minority of naturally occurring acid reflux events is reported as heartburn by the patients. More importantly, in clinical practice, there is a lack of uniformity in perception and description of symptoms induced by reflux events. Whereas some patients describe the classic retrosternal burning sensation that may propagate oral, others describe pressure, pain, discomfort, or even a vague unusual sensation. Whereas, it may be reasonable to assume that the cerebral cortical pain pathways and sensitization of esophageal afferents may be involved, the pathophysiological basis of these different symptoms induced by esophageal acid exposure is not completely elucidated. Indeed, the actual cortical activity associated with heartburn or other symptoms in response to esophageal acid exposure has not been studied to date.

Although animal studies have shown the existence of acid sensitive afferents (9), this finding has only indirectly been confirmed in healthy individuals by documentation of cortical activation in response to esophageal acid infusion without inducing any symptom (27). Many issues regarding esophageal sensory physiology remain uninvestigated, however. With the advent of functional magnetic resonance (MR) imaging (fMRI) of the brain, it is now possible to objectively investigate the esophageal viscerosensation without relying on subjective measurements. For example, studies of healthy individuals using this technique have shown that esophageal acid exposure without inducing any sensation, i.e., subliminal stimulation, results in development of cortical activity (27). These activities due to subliminal/unperceived esophageal acid stimulation are bilaterally distributed over distinct regions of the cerebral cortex including the operculum, superior and medial aspects of the parieto/occipital cortex [Brodmann area (BA) 7 and 30], the anterior (BA 24) and posterior (BA 23) cingulate gyrus, the medial prefrontal region (BA 32), and the insular cortex. Because these activities are induced in the absence of perception, they represent the function of the neurocircuity without the influence of cognitive processes. Previous studies of visceral (3, 29) and somatic pain (18, 19, 35, 40) have identified some of the above-mentioned regions to be part of the cortical pain pathway. Little direct evidence is available about the similarity of cerebral cortical activity associated with liminal/perceived esophageal acid exposure, i.e., heartburn, (26) and subliminal acid stimulation.

In regard to differences between cortical activity during liminal and subliminal visceral stimulation, earlier studies of cortical registration of subliminal and liminal mechanical stimulation of the lower gastrointestinal tract (28) have shown that, although the intensity and volume of the registered fMRI cerebral cortical signals significantly differ between the two stimuli, the areas of activation are comparable. Elucidation of intensity and volumetric and temporal differences between cortical activa-
tion in response to subliminal and liminal esophageal acid stimulation is needed to better understand the complexities associated with perception of esophageal acid exposure.

The aims of the present study, therefore, were to 1) characterize and ascertain the reproducibility of the cerebral cortical representation of heartburn induced experimentally by esophageal acid perfusion in GERD patients, 2) elucidate the differences between these findings and those of subliminal esophageal acid stimulation in healthy controls, and 3) correlate the development of heartburn and cerebral cortical fMRI activity in response to esophageal acid perfusion in GERD patients.

METHODS

Subjects. We studied 11 right-handed volunteer patients (9 male, age range: 30–55 yr) and 15 healthy controls (8 males, 21–49 yr). All patients had a history of daily heartburn. Endoscopy within 3 mo of the present study revealed erosions or ulcerations in seven and no mucosal break in the remaining four patients. At the time of the study, patients were on either proton pump inhibitors (7 patients) or H2 receptor antagonists (4 patients). Studies were approved by the Human Research Review Committee of the Medical College of Wisconsin, and all volunteer patients gave written informed consent before the studies. Some patients had concurrent maladies including hiatus hernia, psoriasis (1 patient), hypertension (6 patients), asthma (2 patients), and gout (1 patient). Healthy controls were recruited by interview as well as following a detailed health questionnaire.

MRI scanning. Gradient echo planar MR images were acquired using a 1.5-Tesla GE Signa System (General Electric Medical Systems, Waukesha, WI) with a custom three-axes head coil designed for rapid gradient field switching and a shielded transmit/receive birdcage radiofrequency coil. The MR scanner and head coil were used to acquire a time course of echo planar images over the entire brain volume. In each of thirteen contiguous 10-mm-thick sagittal slices, 210 images were captured with an echo time (TE) of 40 ms and a repetition time (TR) of 6,000 ms. Echo planar images were 64 × 64 pixels over a 240-mm field of view (in-plane resolution of 3.75 mm). High-resolution spoiled gradient recalled acquisition at steady-state images were also obtained consisting of one hundred twenty-four 1.2-mm-thick slices (TE of 76 ms, TR of 16,000 ms). These high-resolution anatomic images were used for subsequent superposition of cortical activity regions derived from the lower-resolution echo planar blood oxygenation level-dependent (BOLD) contrast image data. All MRI data were stereotaxically transformed to the Talairach-Tournoux coordinate (43) system for comparison and display purposes.

Study protocol. One paradigm-driven (fMRI) scanning sequence was performed in each patient subject on 2 separate days ~1 wk apart. Healthy subjects were studied once during two paradigm-driven fMRI scanning sequences identical to that of GERD patients. Before placing the subjects in the MR scanner, the location of the lower esophageal sphincter (LES) was determined manometrically. A multilumen catheter was inserted transnasally such that a side-hole perfusion port was positioned 15 cm proximal to the LES. A Harvard infusion pump was used to deliver fluid into the esophagus. During a 21-min MR scanning sequence, alternating 5-min intervals of 0.1 N HCl and isotonic saline perfusion followed an initial 1-min interval of saline perfusion. Room temperature acid and saline were perfused at a rate of 1 ml/min. Echo planar MR images were acquired continuously throughout the infusion process at a sampling frequency of 0.17 Hz (TR = 6,000 ms). Subjects were told to rapidly raise and lower the index finger of their right hand to signal a perception of heartburn. The subjects were also asked to rapidly raise and lower the index finger on their left hand to signal the cessation of a heartburn episode. In this way, intervals of perceived heartburn could be temporally logged relative to the MR-scanning sequence by an external observer and later compared with the times of correlated fMRI magnetic signal changes. Whereas any signaling during fMRI studies could be a potential source of fMRI signal change, this type of signaling was chosen because of its simplicity, ease of performance, and reduction in the chance for extensive signal change, with the understanding that any cerebral cortical fMRI signal change associated with a single rapid finger movement would be small compared with the cortical signal changes associated with 5 min of acid perfusion and would occur over a much shorter time frame than those of the perfusion-related cortical response.

Image registration, data analysis, and movement correction. To compensate for subtle changes in head position over the course of the fMRI scanning sessions, an algorithm for three-dimensional (3D) volume registration was used (15). This algorithm is designed to be efficient at fixing motions of a few millimeters and rotations of a few degrees. With the use of this limitation, the basic technique is to align each volume in a time series to a fiducial volume (usually an early volume from the first imaging run in the scanning session). The fiducial volume is expanded in a first-order Taylor series at each point in the six motion parameters (3 shifts, 3 angles). This expansion is used to compute an approximation to a weighted linear least-square fit, where each volume to the data volume is then moved according to the fit, and the new target volume is refit to the fiducial. This iteration proceeds until the movement is small. Effectively, this is gradient descent in the nonlinear least-square estimation of the movement parameters that best make the target volume fit the fiducial volume. This iteration is rapid (usually only 2–4 iterations are needed), because the motion parameters are small. It is efficient, based on a new method using a four-way 3D shear matrix factorization of the rotation matrix. It is also accurate, because Fourier interpolation is used in the resampling process. On the SGI and Intel workstations used for this project, a 64 × 64 pixel × 13 slice volume can be aligned to a fiducial in <1 s.

All fMRI signal analysis were carried out using the Analysis of Functional NeuroImaging (AFNI) software package developed by Robert Cox of the Medical College of Wisconsin and the National Institute of Mental Health (14). This software allows the user to visualize a 3D representation of two-dimensional MRI data in an interactive Unix-based X11 Windows format. In addition to providing a straightforward method for image visualization, the AFNI package also provides the statistical tools for testing the correlation of fMRI signal waveforms to applied stimulation protocols. A nonbiased method of detecting cortical regions that exhibit BOLD changes is achieved by applying a deconvolution and multiple-regression technique that computes the hemodynamic response function from the magnetic signal time series in each voxel and tests whether the response function differs from the response associated with random gaussian variation of the signal (11, 33). A threshold correlation coefficient of 0.7 was used as a limiting criterion for accepting an fMRI time course as being correlated to the stimulus paradigm. Furthermore, we applied an additional clustering requirement that a displayed region of cortical activity must be represented by a cluster of three or more contiguous correlated voxels (8, 25, 28).

AFNI analyses and statistical comparisons were performed on a Pentium III-based PC (Southwest Computers, Houston, TX) with dual-boot capabilities for running both the AFNI software out of a Linux operating system and SigmaStat statistics software (SPSS, Chicago, IL) out of the Microsoft (Redmond, WA) Windows 98 operating system.

Average data in this paper are shown as means ± SE unless otherwise stated. Between-group comparisons of cortical activity were made using unpaired Student’s t-test with Bonferroni correction for multiple comparisons. Intra-group comparison of intensity signal volume and temporal character-
istics of fMRI signals were done using paired Student’s $t$-test with Bonferroni correction. Comparison of the incidence of regional cortical representation in GERD patients and healthy controls was achieved using RxC analysis (42). Reproducibility of fMRI signal time series and cortical topography was tested using analysis of variance and regression analysis as indicated.

RESULTS

Ten of eleven tested patients developed heartburn and exhibited an identifiable change in fMRI signals associated with esophageal acid perfusion. One patient did not develop heartburn during the acid perfusion and did not exhibit changes in fMRI cortical activities. All 15 healthy controls developed cortical fMRI activity without any feeling of heartburn. The total volume of cortical activity induced by esophageal acid perfusion averaged $8,248 \pm 255$ and $7,822 \pm 283 \ \mu l$ in patients and controls, respectively ($P < 0.05$). There were no statistical differences between the distribution of this volume over the right and left hemisphere in either group. In GERD patients, the average time from the onset of acid perfusion to the instant of fMRI signal increase was $1.6 \pm 0.8$ min, whereas the average time from the onset of acid perfusion to the instant of the first report of heartburn was $1.9 \pm 0.6$ min. The average time from the onset of acid perfusion to the onset of fMRI activity in controls ($5.2 \pm 1.7$ min) was significantly longer than that for GERD patients ($P < 0.01$). Figure 1 shows a time line of the fMRI signal events relative to the onset and cessation of acid perfusion. As seen, the fMRI activity for all measured parameters for heartburn occurred significantly earlier than subliminal acid stimuli in healthy controls.

The average maximum percent signal increase in the GERD patients ($16.3 \pm 3.5\%$) was significantly different ($P < 0.01$) than that of the healthy controls ($3.8 \pm 0.9\%$). Figure 2 shows, for a representative GERD subject, a montage of rendered 3D images with a colorized map superimposed to show cortical regions in which BOLD changes were correlated with intervals of esophageal acidification. Table 1 shows the regions of the cortical mantle activated in 10 of 11 GERD patients and 15 healthy controls designated by BA. BA 1–6 represent the primary and secondary sensory/motor cortices. For the representative GERD patient shown in Fig. 2, the voxel in the sensory/motor cortex with the greatest increase in fMRI signal intensity was located at Talairach-Tournoux (43) coordinates $(x = -2, y = -25, z = 54)$. Where these $(x, y, z)$ coordinates are the measurements in millimeters relative to the anterior commissure in the right-left, anterior-posterior, and superior-inferior directions, respectively, BA 7 and 30 are contained in the superior parietal lobule and medial occipital lobe, respectively. For the representative GERD patient shown in Fig. 2, the voxel in the parieto/occipital region with the greatest increase in fMRI signal intensity was located at coordinates $(x = 3, y = -68, z = 37)$. BA 23, 24, and 32 are located in the cingulate gyrus and prefrontal regions. For the representative GERD patient shown in Fig. 2, the voxel in the cingulate gyrus/prefrontal region with the greatest increase in fMRI signal intensity was located at Talairach-Tournoux coordinates $(x, y, z)$. Where these $(x, y, z)$ coordinates are the measurements in millimeters relative to the anterior commissure in the right-left, anterior-posterior, and superior-inferior directions, respectively, BA 7 and 30 are contained in the superior parietal lobule and medial occipital lobe, respectively. For the representative GERD patient shown in Fig. 2, the voxel in the parieto/occipital region with the greatest increase in fMRI signal intensity was located at coordinates $(x = 3, y = -68, z = 37)$. BA 23, 24, and 32 are located in the cingulate gyrus and prefrontal regions. For the representative GERD patient shown in Fig. 2, the voxel in the cingulate gyrus/prefrontal region with the greatest increase in fMRI signal intensity was located at Talairach-Tournoux coordinates $(x, y, z)$.

Fig. 1. The timeline of events from start of intraesophageal acid infusion to return of functional magnetic resonance imagery (fMRI) signal to baseline in gastroesophageal reflux disease (GERD) patients (right) and controls (left). As seen, the subliminal signals from the healthy controls is registered in the cerebral cortex significantly later than liminal signals in GERD patients. Likewise, all of the measured temporal events occur earlier in the GERD patients compared with subliminal events in controls. Values are reported as means ± SE time from the start of acid perfusion.
Table 1. *Esophageal acid perfusion in GERD patients and controls*

<table>
<thead>
<tr>
<th>Brodmann Areas with fMRI Activity</th>
<th>GERD Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>2</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>3</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>4</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>5</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>6</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>7</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>8</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>9</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>10</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>11</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>12</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>13</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>14</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
<tr>
<td>15</td>
<td>X X X X X X X X X X X X X X X X</td>
<td>X X X X X X X X X X X X X X X X</td>
</tr>
</tbody>
</table>

Comparison of the activated Brodmann areas (BA) in response to esophageal acid perfusion in gastroesophageal reflux disease (GERD) patients and healthy controls. As seen, the number of BA in the sensory motor cortex (BA 1–6) among GERD patients with liminal/perceived esophageal acid exposure was substantially more than that of the healthy controls with subliminal acid stimulation without developing heartburn. Comparing the volumes of functional magnetic resonance imagery (fMRI) activity between controls with sensory/motor activity (871 ± 96 μl) and GERD patients with sensory/motor activity (1,480 ± 197 μl) showed significantly greater volumes of regional cortical recruitment among GERD patients (P < 0.01). O, operculum region; I, insular region.
and temporal lobes adjacent to the lateral sulcus overlies the insular region. For the representative GERD patient shown in Fig. 2, the voxel in the operculum with the greatest increase in fMRI signal intensity was located at Talairach-Tournoux coordinates \((x = 55, y = 11, z = 7)\).

Reproducibility of cortical representation of heartburn. The cortical fMRI signal changes associated with intraesophageal acid perfusion during studies 1 and 2 were compared for volume of activated voxels, maximum signal intensity, activated BAs, and correlation of activity during two studies at the same time points. Total volume of cortical activity as well as volume of voxel activity in each hemisphere was similar for both studies (Fig. 3). Using analysis of variance, voxel by voxel comparison of normalized correlation coefficients of cortical fMRI activity showed no significant difference between the two study sessions in each patient. The maximum average percent fMRI signal change from baseline during studies 1 and 2 (16.3 ± 3.5 and 16.7 ± 4.7%, respectively) were similar. Table 2 shows the BAs activated during each study session. Among the 10 patients who exhibited cortical fMRI activity, in seven, the same (100%) BAs were activated in both studies. In one subject, 56% of the BAs were activated in both studies, in two patients, 90% of BAs were activated in both studies, and in only one subject, 90% of BAs were activated in both studies (Fig. 5). Representative examples of cerebral cortical fMRI activity during studies 1 and 2 in the same subject are shown in Fig. 6.

The temporal characteristics of fMRI signal activation and deactivation during the two study sessions and their comparison with those of subliminal acid stimulation in healthy controls are shown in Table 3. As seen, whereas the temporal characteristics of fMRI during liminal/perceived esophageal acid perfusion during the two study sessions were virtually identical, these characteristics in GERD patients were significantly different from those of subliminal acid stimulation in healthy controls (\(P < 0.01\)).

**DISCUSSION**

In this study, we determined the cerebral cortical representation of heartburn among patients with GERD and ascertained its reproducibility. We also compared the findings with those of cortical representation of subliminal esophageal stimulation induced by acid perfusion in healthy asymptomatic individuals. Within the confines of the resolution of the fMRI technique used, study findings indicate that the cortical topography of heartburn associated with esophageal acidification in GERD patients is similar to that of healthy subjects developing a subliminal response to esophageal acid infusion, except for inconsistent activation of some areas of the sensory motor cortex in the latter group. This topography involves the sensory motor cortex, cingulate gyrus, prefrontal cortex, and parieto-occipital regions, as well as the insula. It is important to recognize that because of the voxel size in this study, subtle differences in the magnitude of involvement in each of the activated regions between the two groups might have been obscured.

**Table 2. BAs with fMRI Activity in Studies 1 and 2**

<table>
<thead>
<tr>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodmann Areas with fMRI Activity</td>
<td>Brodmann Areas with fMRI Activity</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Among the 130 cells of the table representing the BAs and the insula, only 10 cells were different between studies. This represents a concordance of 92% between the activated BAs during the 2 studies.
Primary and secondary somatosensory cortices receive transmission from the thalamus relaying noxious as well as innocuous sensory input (37, 41). Previous studies have shown the activity of primary and secondary sensory cortices associated with both somatic (10) and visceral (8) pain as well as nonpainful visceral sensation (2, 4). The evidence from these studies points to the discriminative function of this region, including the spatial, temporal, and intensity aspect of the pain in determining the possibility of injury due to painful, or potentially painful, stimuli (10). Although there is no direct evidence from the present study to ascertain the function of the somatic sensory cortex during esophageal acidification, on the basis of the above information, one could infer that its activation is associated with the sensory-discriminative aspect of heartburn perceptions in GERD patients. Activation of the primary somatic sensory cortex has been inconsistently observed in somatic pain studies (36). This finding has been attributed to the differences in the size of the stimulated area and temporal summation rather than the intensity of the stimulus (36). Contrary to the moderately painful stimuli, stimulus just above the pain threshold has been reported to fail to activate the primary somatosensory cortex (21). In the present study, this type of activity was present in only one of 15 controls (6%) but in 7 of 11 (66%) GERD patients. These findings are in concordance with previous reports about somatic pain and activation of primary somatosensory cortex.

Findings of the present study also indicate the activation of other brain regions, such as the anterior cingulate, prefrontal, and insular cortices during perception of esophageal acid exposure. These findings support the fact that the cardinal symptom of GERD, i.e., heartburn, shares the central processing pathways of somatic (13, 16, 45) and visceral (3, 5, 8, 31) pain. Nociceptive neurons contained in the medial thalamic nuclei project to the anterior cingulate cortex (2, 17, 31). In humans, painful stimuli have been found to evoke potentials in the anterior cingulate (30). The data are believed to indicate (24) involvement of the anterior cingulate in pain processing in addition to its role in cognitive processes such as attention (18, 22). Similarly, previous studies documented direct thalamocortical nociceptive input to the insular cortex (20, 23). The insula is believed to be involved in the affective aspect of pain in addition to its role in autonomic control (24). Insular lesions result in atypical behavioral and physiological responses to painful stimuli, whereas pain sensation appears to remain normal (7, 34). These changes in physiological and behavioral response have been attributed to abnormal processing of the affective component of the stimulus (24). Activation of the central pain processing pathway with subliminal acid stimulation as well as its involvement in perception of esophageal acid exposure was shown in Fig. 5.

Fig. 4. Average fMRI signal change from baseline in esophagitis patients in response to intraesophageal acid infusion during studies 1 (A) and 2 (B). There were no statistical differences between %fMRI signal changes between studies 1 and 2 at comparable 6-s intervals during intraesophageal acid infusion. The stimulus paradigm is shown in gray, the lower plateau of the gray line being associated with saline perfusion and the higher plateau being associated with acid perfusion.

Fig. 5. Correlation of time-matched %fMRI signal change waveforms between studies 1 and 2. Average fMRI activity at comparable temporal points from the 2 studies were significantly correlated (r = 0.86; P < 0.001). Average time-matched fMRI signal changes are shown as ●. As seen, the slope of the regression line is indistinguishable from unity.
pain, discomfort, etc. encountered in clinical practice, such as a burning sensation, acid exposure can explain some of the variability in the description of the sensation induced by acid reflux in GERD patients encountered in clinical practice, such as a burning sensation, pain, discomfort, etc.

In addition, study findings indicated that the cortical response associated with heartburn is significantly faster and the increase in fMRI magnetic signal intensity is significantly greater in GERD patients compared with healthy subjects. Although the reason for these differences is not currently known, the following possible explanations can be proposed. The differences in fMRI signal timing are due to the differences between the GERD patients and controls in the time needed for the acid stimulus to reach the esophageal afferents transmitting the stimulus signal. In that, in GERD patients, the afferents are more accessible to the infused acid compared with healthy controls due to impaired esophageal epithelial barrier function in GERD patients (12). With regards to differences in the intensity of fMRI signals, these differences could represent prior sensitization (38, 39) of the esophageal afferents in GERD patients. Alternatively, differences between healthy controls and GERD patients in neutralization of the defusing acid through the mucosal layer by function of esophageal mucus and bicarbonate-secreting glands before the acid reaches the afferents can also explain the observed differences in the intensity of fMRI signals, in that among GERD patients, the intensity of acid stimulation could have been higher due to less neutralization because of diminished bicarbonate/mucus secretion in this group.

Study findings also demonstrate that the topography, volume, and intensity of cortical registration of heartburn induced by esophageal acid exposure to a defined acidity for a defined period of time are quite reproducible. It is anticipated, based on experiments of the lower gut using graded mechanical stimulation (28), that variation of acid normalcy and/or exposure time may induce different volumes and intensity of cortical activity. These experiments, however, were not part of the present study.

A review of the BAs activated during the experience of heartburn reveals similarities of these areas with those activated by balloon distention of the lower gut (28). These findings suggest the recruitment of a common central pain-processing pathway for sensory signals originating from the intestine and also suggest that perception of a gastrointestinal symptom such as heartburn, pressure, or pain as a result of a given stimulus is not stimulus specific, but rather the result of cognitive discriminations from a common pool of registered information. The nonspecific cortical registration has also been previously demonstrated for volitional motor tasks involving deglutition, where areas of cortical activation during volitional swallow have been reported to be similar to those of swallowing components such as volitional tongue rolling, lip pursing, and jaw clenching (25). These findings, however, may simply be due to low resolution of the fMRI technique currently used. It is possible that with higher temporal and anatomical resolutions, possible differences in various regions of interest may become evident.

In conclusion, the cortical activity associated with liminal/perceived esophageal acid exposure in GERD patients 1) shares similar regions with unperceived/subliminal acid stimulation in healthy controls and involves multiple cerebral cortical regions including the insular cortex, prefrontal/anterior cingulate gyrus, parietooccipital, and sensory/motor cortices and 2) occurs more rapidly and with greater intensity than the activity measured in healthy controls in response to subliminal esophageal acid exposure. The cerebral cortical fMRI activity exposure can explain some of the variability in the description of the sensation induced by acid reflux in GERD patients encountered in clinical practice, such as a burning sensation, pain, discomfort, etc.
regions associated with esophageal acidification suggest involvement of cortical pain processing pathways in perception of esophageal acid exposure and may explain the variations encountered in clinical practice defining this sensation.

ACKNOWLEDGEMENT
This work was presented as a poster at the American Gastroenterological Association’s Digestive Disease Week, 1999, New Orleans, LA.

GRANTS
This work was supported in part by National Institutes of Health Grant R01 DC-00669.

REFERENCES

AJP-Gastrointest Liver Physiol • VOL. 286 • JANUARY 2004 • www.ajpgi.org

CORTICAL REPRESENTATION OF HEARTBURN

G181

Downloaded from http://ajpgi.physiology.org/ by 10.220.33.4 on June 25, 2017