Real-Time Imaging of Human Cortical Activity Evoked by Painful Esophageal Stimulation

ANTHONY R. HOBSON*,†  PAUL L. FURLONG,‡  SIAN F. WORTHEN,*†  ARJAN HILLEBRAND,†  GARETH R. BARNES,†  KRISH D. SINGH,†  and QASIM AZIZ*

*Section of GL Science, Division of Medicine & Neurosciences—Hope, University of Manchester, Hope Hospital, Salford, Lancashire; and †Wellcome Trust Laboratory for MEG Studies, Neurosciences Research Institute, Aston University, Birmingham, United Kingdom

Background & Aims: Current models of visceral pain processing derived from metabolic brain imaging techniques fail to differentiate between exogenous (stimulus-dependent) and endogenous (non–stimulus-specific) neural activity. The aim of this study was to determine the spatiotemporal correlates of exogenous neural activity evoked by painful esophageal stimulation. Methods: In 16 healthy subjects (8 men; mean age, 30.2 ± 2.2 years), we recorded magnetoencephalographic responses to 2 runs of 50 painful esophageal electrical stimuli originating from 8 brain subregions. Subsequently, 11 subjects (6 men; mean age, 31.2 ± 1.8 years) had esophageal cortical evoked potentials recorded on a separate occasion by using similar experimental parameters. Results: Earliest cortical activity (P1) was recorded in parallel in the primary/secondary somatosensory cortex and posterior insula (~85 ms). Significantly later activity was seen in the anterior insula (~103 ms) and cingulate cortex (~106 ms; P = .0001). There was no difference between the P1 latency for magnetoencephalography and cortical evoked potential (P = .16); however, neural activity recorded with cortical evoked potential was longer than with magnetoencephalography (P = .001). No sex differences were seen for psychophysical or neurophysiological measures. Conclusions: This study shows that exogenous cortical neural activity evoked by experimental esophageal pain is processed simultaneously in somatosensory and posterior insula regions. Activity in the anterior insula and cingulate—brain regions that process the affective aspects of esophageal pain—occurs significantly later than in the somatosensory regions, and no sex differences were observed with this experimental paradigm. Cortical evoked potential reflects the summation of cortical activity from these brain regions and has sufficient temporal resolution to separate exogenous and endogenous neural activity.

Attempts to develop a comprehensive model of visceral pain processing go back more than a century,1,2 and this remains a fundamental goal for researchers endeavoring to differentiate between specific mechanisms of aberrant pain processing in patients with functional gastrointestinal disorders (FGDs). The perception of pain and our subsequent interpretation of and emotional responses to its occurrence are a result of neural activity generated in a matrix of cortical and subcortical structures.3–5 Pain is commonly caused by tissue-damaging stimuli; however, FGD patients commonly report pain in the absence of any known structural or biochemical abnormality.6 Our ability to understand the etiology of anomalous pain in this group of patients would be enhanced if the functional properties of the nociceptive pathways and brain regions involved in visceral pain processing could be delineated.

Most of our knowledge regarding the activation of visceral nociceptive afferents and the ensuing transmission of this information to the brain comes from animal studies.7 Progression of the model to incorporate the subsequent processing of visceral pain within the brain predominantly requires studies in humans. Functional brain imaging has greatly enhanced our ability to evaluate this pain-related cortical activity.5,8–13 Techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have allowed researchers to study the neuroanatomic representation of cortical pain processing, and elegantly designed experimental paradigms have started to show the functional relevance of these cortical regions to different aspects of the pain experience.14–17 Although PET and fMRI have shown many salient features of pain processing, these techniques do not have sufficient temporal resolution to map cortical activity as it dynamically changes on a millisecond-by-millisecond basis. This is important because exogenous (stimulus-dependent) and endogenous (non–stimulus-specific) components of pain processing occur in different temporal time windows.18

Abbreviations used in this paper: CEP, cortical evoked potential; FGD, functional gastrointestinal disorder; MEG, magnetoencephalography; PET, positron emission tomography; ROI, region of interest; SAM, synthetic aperture magnetometry; VAS, visual analogue scale.

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Differentiation of the 2 requires real-time recording of neural activity, and, therefore, it would be beneficial to identify the temporal sequence of neural activation within the visceral pain matrix.

After a sensory event in any modality, transient fluctuations in the brain’s neural activity occur. These fluctuations result from an increase of synchronized postsynaptic activity in a large number of neurons, which generate a summated extracellular electromagnetic field. The electrical component of this neural activity is volume conducted to the scalp and can be recorded with millisecond temporal resolution via scalp electrodes. These event-related fluctuations are relatively small in comparison to ongoing background brain activity, but if consistent, repetitive stimuli are delivered, then the subsequent data can be averaged to show a stimulus-specific cortical evoked potential (CEP) with elimination of the background noise. In visceral pain research, CEP has been used to investigate the processing of visceral sensation, and experimental parameters have been established that result in highly reproducible recordings. A limitation of CEP is that the electrical signal from active cortical neurons becomes distorted and attenuated when it passes through the structures that lie between the cortical source and recording electrodes. This limits our ability to accurately identify the cortical regions involved in the generation of visceral CEP.

The magnetic field that is generated by active cortical neurons can be also be detected outside the skull by using a technique called magnetoencephalography (MEG). The ability of MEG to accurately identify the loci of cortical activity is comparable to that of PET and fMRI; however, neural activity is recorded with millisecond temporal resolution. MEG has an additional advantage in that the recorded signal represents the magnetic component of the electromagnetic field generated by neuronal activity and is directly related to the scalp recorded electrical CEP response. Consequently, data obtained with MEG can help us to identify the cortical regions involved in the generation of the scalp recorded CEP response.

The primary aim of this study was to determine the temporal sequence of cortical activation after painful esophageal stimulation. Secondary aims were to examine sex differences and compare MEG responses with those obtained by using CEP to elucidate the spatial correlates of each CEP component.

**Materials and Methods**

**Subjects**

We recruited 16 healthy volunteers (8 men; mean age, 33.8 ± 2.2 years). All were free of any gastrointestinal, cardiac, or neurological disorders, and none was taking any medication at the time of the study. Informed written consent was obtained from all volunteers, and the local ethics committee approved the experimental protocols.

**Electrical Stimulation**

Esophageal electrical stimulation was performed by using a pair of platinum bipolar ring electrodes (2-mm electrodes with an interelectrode distance of 1 cm) sited 5 cm from the tip of an intraluminal catheter (external diameter, 3 mm). The catheter was constructed from nylon tubing covered with stainless-steel braid and sheathed in silicone rubber (Gaeltec; Dunvegan, Isle of Skye, Scotland, UK).

The electrodes were connected to a constant-current, high-voltage stimulator (model DS7; Digitimer Ltd., Welwyn Garden City, Herts, UK) and externally triggered (model DSN; Digitimer Ltd.). The interelectrode impedance was monitored throughout to ensure mucosal contact, and the epoch was rejected if mucosal contact was shown, as assessed via an impedance monitor, to be inadequate (>10 kΩ). The stimuli were 200-μs square-wave pulses, and we used a maximum intensity of 100 mA. These stimulation parameters have been used in several previous studies and do produce adverse cardiac events.

**Magnetoencephalography**

MEG was recorded with a 151-channel whole-cortex system (Omega; CTF Systems Inc., Vancouver, BC, Canada), and recordings were made inside a shielded room. MEG data were collected with third-order gradiometers and digitized at a sampling rate of 625 Hz. Data acquisition was time-locked to an external trigger. The data were initially acquired with open filters (0–200 Hz), and after acquisition, individual epochs were removed from the dataset if eye-movement artifacts were evident.

After data acquisition, MEG data were co-registered with the subject’s anatomic magnetic resonance scan by first using a 3-dimensional digitizer (Polhemus Isotrak System; Kaiser Aerospace Inc., Colchester, VT) to digitize the subject’s head shape and then by matching the digitized surface to a head shape extracted from the subject’s anatomic MRI scan by using an align algorithm.

**Synthetic Aperture Magnetometry**

The MEG data were analyzed with synthetic aperture magnetometry (SAM), which is an adaptive beam-forming technique. With SAM, each 5-mm³ voxel of the brain is linked to the 151-channel MEG detector array by using an optimal spatial filter. The MEG data are then projected through this spatial filter to give a measure of current density as a function of time for each target voxel. In effect, this creates a virtual depth electrode in each 5-mm³ brain area. Subsequent analysis of these data allows comparison of power changes in active and passive epochs in much the same way as PET and fMRI studies. This allows construction of neural activity index maps that depict group average differences between states, which are then superimposed onto an anatomic MRI scan. However, in
this study, because the primary aim was to delineate the temporal sequence of cortical activity, we merely used the SAM analysis technique to create a set of spatial filters for our subsequent region-of-interest (ROI) analysis. Further technical details regarding SAM can be obtained from 2 review articles.

**Virtual Electrode Region-of-Interest Analysis**

To explore the temporal dynamics of cortical activation in each subject, arrays of virtual electrodes were placed bilaterally at 1.5-cm intervals in the following ROIs:

1. Superior to inferior along the postcentral gyrus extending from the primary somatosensory cortex (S1) into the anatomic regions previously ascribed to the secondary somatosensory cortex (S2)/posterior insula.
2. Posterior to anterior along the sylvian fissure in the anatomic region of the insula.
3. Anterior to posterior from the perigenual to posterior cingulate cortex.

All ROIs were chosen because they were the anatomic regions most consistently described in previous visceral pain studies.

Virtual electrode positions were obtained from each subject’s co-registered anatomic MRI scan, and the SAM weighting matrix was calculated to design an optimal spatial filter for each electrode position, thus improving the signal–noise ratio. This weighting matrix was used to calculate the unaveraged current source signal from each brain region. Because data collection was both time- and phase-locked to the stimulus, signal averaging was used to further improve signal to noise. This generated an event-related MEG response for each virtual electrode position in each of the subject’s 2 datasets. This approach has recently been used in a study to determine the sensorimotor representation of the pharynx. The latency of the MEG responses was then calculated and used to elucidate the temporal sequence of activation. The 3 ROIs were then divided into 8 subregions derived from the pain literature, to simplify analysis. These were the topographic region of S1 corresponding to the trunk, the topographic region of S1 corresponding to the intra-abdominal area, S2, posterior insular, anterior insula, perigenual cingulate, midcingulate, and posterior cingulate.

**Esophageal Cortical Evoked Potentials**

Esophageal CEPs were recorded by using 2 silver/silver chloride surface electrodes that were applied to the scalp with electrode paste (Elefix; Nihon Kohden, Tokyo, Japan). By using the international 10-20 system of electrode placement, the active electrode was positioned at the vertex, and the reference electrode was positioned on the left earlobe. An additional ground electrode was positioned on the neck. Recordings were performed in a quiet room with the subject semirecumbent, awake with eyes open, and asked to minimize eye movements and swallowing.

The data were acquired with a CED 1902 programmable signal conditioner (Cambridge Electronics Design Ltd., Cambridge, UK). Display and analysis used the SIGAVG program version 6.04 and Signal for Windows version 1.72 (Cambridge Electronic Design). The amplifier gain was set at 100,000, and the recording sensitivity was 25 μV. The bandpass filter settings were 1–100 Hz, and a noise-reduction device (Humbug; Digitimer Ltd.) was used, when needed, to reduce interference from the main electrical supply.

The sampling rate was set at 4000 Hz, and the recording epoch was 1 second long. The first 200 ms of the epoch was prestimulation time. Each individual epoch was saved, and the average of the run could be viewed during acquisition. An automatic artifact-rejection facility was used to prevent contamination from eye blinks and swallows. Before each recording, scalp electrode impedance was reduced to < 3 kΩ by applying a preparation paste (Omniprep; Weaver & Co., Aurora, CO).

**Experimental Protocol 1: Magnetoencephalography**

The location of the lower esophageal sphincter in relation to the incisors had previously been determined by esophageal manometry in all subjects. Subsequently, the stimulation catheter was positioned perorally or nasally into the esophagus so that the electrode pair was situated 5 cm proximal to the lower esophageal sphincter.

Subjects had 2 recording runs of 50 stimuli applied at a frequency of 0.2 Hz and with an interrun interval of 10 minutes. For each run, pain thresholds to electrical stimulation were determined by increasing the intensity in increments of 2 mA until a score of 7.5 was reached on a visual analogue scale (VAS) (0, no pain; 10, severe pain). This was repeated 3 times, and the mean of these readings was taken as the average pain threshold. These parameters have been previously shown to be optimal for obtaining highly reproducible esophageal CEP and ensured that the perceived pain intensity remained constant across subjects. Verbal pain descriptors were also documented after each run.

After each run, the subject scored the intensity of the stimulus again by using the VAS. After each recording session, each subject’s head shape was digitized for subsequent co-registration with the anatomic MRI scan.

**Experimental Protocol 2: Esophageal Cortical Evoked Potentials**

Esophageal CEPs to electrical stimulation were recorded from 11 subjects (6 men) who had also participated in protocol 1. The average of 200 stimuli was acquired in 4 runs of 40 stimuli, and a 10-minute rest period was left between runs. Stimulation was performed at a frequency of 0.2 Hz and at an intensity that produced 7.5 on the pain VAS scale. After each run, the subject was asked to record his or her perceived level of intensity on the VAS scale, and verbal pain descriptors were documented.
Data and Statistical Analysis

Temporal differences were observed between the activation of the 2 hemispheres, but these latencies were not specific to the left or right hemisphere. Consequently, the data were separated into first-hemisphere activity (ie, the hemisphere that was activated earliest) and second-hemisphere activity (ie, the hemisphere that was activated latest). To compare sex differences, as well as provide overall group values, we first separated the analysis groups into men and women, and then, if there were no significant differences, data were pooled. Activations were directly compared for men and women and for the first and second hemispheres, and the activation of each brain region was compared with that of all other regions. Several within-group analyses were performed by using the first peak activity and the total duration of activity from each brain region. The significance of any observed difference in mean values was assessed with the Friedman nonparametric test for related samples. Post hoc analyses were performed with the Fisher least significant difference test, which corrected for multiple comparisons.

The laterality of cortical activity was determined on the basis of differences in the first peak activity between comparable cortical regions. If the latency difference was ≤5 ms, then activation was denoted as bilateral. If the latency difference was >5 ms, then the hemisphere that showed earliest activation was deemed as the dominant or first hemisphere.

When comparing data between the MEG and CEP studies, a Shapiro–Wilk test of normality was used to determine the distribution of the data. If data were normally distributed, then a Student t test was used; if not, a nonparametric Mann–Whitney test was used. All data in tables and graphs are given as group means ± SD.

Results

There was no significant difference in the age of our male and female subjects (female, 29.4 ± 7.6 years; male, 30.8 ± 2.9 years; P = .66) enrolled in the combined study.

Character, Referral Pattern, and Intensity of Esophageal Pain

The most commonly chosen words to describe pain elicited by electrical stimulation of the esophagus were burning, aching, stabbing, and dull, and the pain was referred retrosternally, over the lower chest wall. Values for mean intensity of stimulation and VAS scores for men, women, and pooled overall data are given in Figure 1. It can be seen that there were no significant differences between sexes for either the intensity of the stimulation or the subjective VAS score. In addition, there were no differences between intensities and VAS scores when data from the 2 experimental protocols were compared.

Laterality of Cortical Activity

Details of laterality for the group as a whole are given in Figure 2. It can be seen that for most regions, more subjects had a left-sided dominance. However, activity in the posterior cingulate was generally equivalent bilaterally.

Magnetoencephalographic Data

Neural activity in the S1 trunk, S1 abdominal, S2, and posterior insula occurred in parallel with the first peak (P1) occurring approximately 80–85 ms after esophageal stimulation. There were no significant differences in the P1 latency within these 4 regions between men and women. P1 latency in the anterior portion of the insula was significantly delayed in comparison to P1 latency in these 4 other somatosensory regions (103 ± 22 ms vs 82.5 ± 11 ms; P = .0001), and, once again, there were no differences between male and female subjects (Figure 3).
The P1 latency of neural activity in the perigenual, mid, and posterior cingulate was significantly delayed when compared with S1, S2, and posterior insula (Figure 3), and this was consistent for male and female subjects. There were no differences in the P1 latency of activity in the anterior insula when compared with each of the 3 cingulate regions. When male and female data were pooled, the P1 latency in the mid-portion of the cingulate was significantly earlier than that seen in either the perigenual or the posterior cingulate regions (95.6 ± 11 ms vs. 104.7 ± 15 ms and 106.5 ± 22 ms; P = .01 and .04). Figures 4 and 5 show MEG responses from a single virtual electrode placed in each of the 8 cortical regions in 1 male and 1 female subject.

**Esophageal Cortical Evoked Potentials**

Esophageal CEPs consisted of the characteristic triphasic P1, N1, and P2 complex, and the morphology was similar for male and female subjects. There was also a late response that was more variable among subjects, and this most likely reflects an endogenous response that has been described in previous studies. Values for the latency of P1, N1, and P2 peaks can be seen in Table 1.

**Comparison of Magnetoencephalographic and Cortical Evoked Potential Data**

Table 2 shows comparative data in subjects who had both MEG and CEP data acquired between the first peak latencies (P1) of the esophageal CEP response and the earliest peak response obtained with MEG calculated as mean peak latency from responses recorded in S1, S2, and posterior insula. There were no significant differences between the P1 latency of the CEP and MEG responses for male (P = .1), female (P = .9), or overall pooled data (P = .16) in the 11 subjects studied.

The total duration of cortical activity recorded after esophageal stimulation was significantly longer when CEPs were compared with MEG (overall group data: CEP, 593.96 ± 58 ms; MEG [value was taken from the posterior cingulate because this region was active longest in the MEG study], 525 ± 13 ms; P < .0001). Data for the duration of neural activity in all brain regions are given in Table 3. A representative CEP response from 2 male and 2 female subjects can be seen in Figure 6.

**Discussion**

The MEG data described herein show for the first time that, after painful electrical stimulation of the esophagus, neural activity initially occurs in parallel within the primary (S1) and secondary (S2) somatosensory cortex and the posterior region of the insular cortex. After this, neural activity is observed within the anterior portion of the insular cortex and throughout the cingulate cortex. Activity in the mid-portion of the cingulate cortex occurs significantly earlier than that observed in either the perigenual or posterior regions of the cingulate. When data obtained from male and female subjects were compared, we found no significant differences in either the psychophysical measures or the observed temporal neural activation patterns. When P1 latencies obtained by both techniques were compared, there were also no significant differences. The major difference seen between modalities was in the duration of recordable neural activity, which was significantly longer with CEP, and possible reasons for this are discussed in detail below.

**Figure 2.** Laterality of cortical activation. This figure shows which cortical hemisphere showed the earliest neural activity as determined from the peak latency of the MEG response. When the latency difference between hemispheres was <5 ms, activation was deemed bilateral. Data reflect both male and female subjects.

**Figure 3.** P1 latencies from S1, S2, insula, and cingulate cortices. This figure shows values for the P1 latency of the MEG response from the cortical hemisphere that showed the earliest neural activity. Values are given in milliseconds for male, female, and overall data. Data are displayed as group mean ± SD. Statistical comparison between male and female data showed no significant differences. *Significant increase in the P1 latency from the anterior insula and 3 cingulate regions when compared with somatosensory regions (P = .0001); #significantly decreased latency of the P1 latency from the midcingulate when compared with the 2 other cingulate regions when male and female data were pooled (P = .04).
Our data show that the early P1 component of the CEP response occurs in the same temporal window in which neural activity is first recorded in parallel in somatosensory and posterior insula regions, whereas the subsequent N1 and P2 components most likely reflect an amalgamation of neural activity throughout all of the brain regions investigated in this study. This triphasic complex seems to reflect the exogenous components of event-related neural activity, because we have previously shown that these are highly sensitive to changes in the characteristics of the sensory stimulus. The later response observed in the CEP study most likely reflects the endogenous components of esophageal cortical pain processing, which represents engagement of higher-order functional specificities of pain perception, such as cognition, attention, and behavioral responses. These endogenous potentials can be obtained in response to many stimulus modalities but were not detectable by using this novel application of MEG. This may reflect the fact that they represent a summation of neural activity generated by multiple cortical regions, many of which were not studied here with MEG, and, subsequently, the CEP response, which reflects the volume-conducted summation of all cortical activity, may be better suited to record endogenous components when compared with the spatially filtered MEG response used in this study. This fact is supported by the fact that conventional MEG using dipole analysis has been successful in recording such components.

Figure 4. This figure shows MEG responses from 1 male (left) and 1 female (right) subject taken from representative virtual electrode positions placed in S1, S2, and insula cortices. It can be seen that the first peak (P1, either positive or negative) in the first 4 cortical regions occurs at the same latency. However, the first peak in the anterior insula (bottom trace) has a longer latency. This was consistent for both male and female subjects. Virtual electrode positions are shown via the crosshairs by using a representative anatomic magnetic resonance scan. The scale on the x-axis is in milliseconds, and the y-axis is in nanoampmeters. The black dotted line represents the stimulus onset, and the gray dashed line indicates the approximate first peak (P1) latency.

Figure 5. This figure shows representative MEG responses from 1 male (left) and 1 female (right) subject taken from representative virtual electrode positions placed in the perigenual (top trace), mid (middle trace), and posterior (bottom trace) cingulate. It can be seen that the first peak (P1, either positive or negative) in these 3 regions occurs at a similar latency. Virtual electrode positions are shown via the crosshairs by using a representative anatomic magnetic resonance scan. The scale on the x-axis is in milliseconds, and the y-axis is in nanoampmeters. The black dotted line represents the stimulus onset, and the gray dashed line indicates the approximate first peak (P1) latency.
The ability to separate out the exogenous and endogenous cortical responses to stimuli is novel to MEG/CEP and has several advantages in that exogenous components, by their very nature, appear only when a stimulus is applied. Hollerbach et al. have shown this previously, showing that CEP responses to anticipated esophageal stimuli produce endogenous (late) but not exogenous (early) responses, whereas responses to actual esophageal stimuli contain both. The importance of dissociating these 2 components has been further illustrated in a recent fMRI study by Derbyshire et al. which showed that the brain areas activated by heat pain can also be activated by hypnotically suggested pain in the absence of any peripheral stimuli. The ability of the human brain to activate the cortical pain matrix in response to anticipated painful esophageal distention has also been shown in an fMRI study that used a classical conditioning paradigm. Taken together, these studies suggest that the results of imaging studies from techniques such as PET and fMRI may reflect a combination of endogenous and exogenous neural activity, and currently they do not have sufficient temporal resolution to resolve this. In contrast, the exogenous components recorded with MEG and CEP described herein seem to be, at present, the most appropriate and reliable method of assessing the transmission, afferent pathway sensitivity, and subsequent stimulus-specific processing of esophageal and other types of experimental visceral pain.

No sex differences in psychophysical and neurophysiological responses to esophageal stimulation were observed in this study. A review of the literature by Berkley documents many observed differences between male and female pain responsiveness. Most notably, the findings of Berkley’s review reported that females generally report lower pain thresholds and rate stimuli as more painful or have less tolerance for intense stimuli. Many factors, such as temporal summation, spatial extent and locality, sex of the experimenter, attractiveness of the experimenter, and period of the menstrual cycle, to name but a few, may affect reported pain thresholds, and these data are supported in studies of gastrointestinal pain. The stimulus used in our study was a brief, single-pulse electrical stimulus and primarily allowed us to record the early stages of esophageal pain processing. These parameters are probably not well suited to explore sex differences such as those described previously, which may primarily be modulatory and may not appear as readily in such a short temporal window as that used in MEG and CEP studies.

Another aim of the study was to use the temporal information obtained with MEG to improve our understanding of cortical visceral pain processing. We first

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<th>Table 1. Esophageal CEP Latencies</th>
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<td>P1</td>
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<td>N1</td>
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<td>P2</td>
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NOTE. This table shows the latencies of the esophageal CEP components for male and female subjects in addition to the overall pooled data. Statistical comparisons were performed between male and female subjects for each component, and no significant differences were seen. Data are displayed in milliseconds ± SD.

<table>
<thead>
<tr>
<th>Table 2. Comparison Between First Peak Latencies for CEP and MEG</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Male (n = 6)</td>
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<td>Female (n = 5)</td>
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<td>Overall (n = 11)</td>
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NOTE. This table shows values for latency (milliseconds) of the first peak latency of the cortical response as recorded with esophageal cortical evoked potentials (CEP) and magnetoencephalography (MEG). All values are group means ± SD.

<table>
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<th>Table 3. Duration of Cortical Activity</th>
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<td>Brain region</td>
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<td>S1 trunk</td>
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<td>S1 abdomen</td>
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<td>S2</td>
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<td>Posterior insula</td>
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<td>Anterior insula</td>
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<td>Perigenual cingulate</td>
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<td>Mid cingulate</td>
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<td>Posterior cingulate</td>
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NOTE. This table depicts the total duration of neural activity from each cortical region within the cortical hemisphere that was first activated (first hemisphere) and the cortical hemisphere that was subsequently activated (second hemisphere). Data are group means of all 16 subjects and are displayed in milliseconds ± SD.

![Figure 6](image_url)
separated the S1 response into 2 regions that corresponded to the homuncular representation of the intra-abdominal and trunk regions. We were then able to show that responses in the intra-abdominal S1, S2, and posterior insula were temporally indistinguishable from one another, thus confirming data from recent studies that have given this region the encompassing name of the operculainsular cortex, because its role in pain processing currently can be separated by neither anatomy nor function. Activation in the operculainsular cortex was bilateral, with a mean latency difference of ~10 ms between hemispheres: this is similar to the latency difference of 5–15 ms seen in somatic pain studies.43,44

Activation in the trunk S1 was more asymmetrical, with a mean latency difference between hemispheres of ~20 ms. This asymmetrical representation in the trunk region of S1 is consistent with previous PET and fMRI studies of the esophageal sensation10,11 and may reflect the fact that the esophagus is a midline structure with bilateral but asymmetrical cortical representation similar to the cortical representation of other midline structures such as the pharynx.45,46

Peak latencies in the anterior insula were significantly longer (~25 ms) than those recorded in the posterior insula. This difference in the temporal sequence of activation between these 2 insula regions may be partly explained by studies that have used intracortical electrode recordings in patients with temporal lobe epilepsy. These studies have shown that the posterior/midinsula region is part of a somatic sensory network involved in processing painful and nonpainful somatic sensations.47,48 In contrast, stimulation of the anterior insula in the same subjects elicited visceral sensitive and visceral motor responses, thus indicating that the anterior insula is part of a visceral sensorimotor network.47,48 In addition, MEG latencies recorded from virtual electrodes placed in the perigenual cingulate were similar to those obtained from the anterior insula. Animal studies have previously shown that afferents from the anterior insula project to areas 24a (perigenual) and 24b (mid) of the cingulate cortex.49 A recent study that examined the effects of emotional context on visceral sensory processing showed increased activation of the anterior insula and dorsal cingulate cortex when esophageal stimulation occurred while the subject was observing fearful facial expressions.16 Taken together, these findings suggest that, although the posterior and anterior insula have dense reciprocal connections,9 the considerable latency difference seen between these 2 regions probably reflects their respective roles in processing different aspects of the pain experience. We have also shown that the first peak latency within the mid anterior cingulate cortex was ~96 ms, and later activity occurred in the perigenual and posterior regions. The fact that the cingulate cortex is activated later than the somatosensory regions is consistent with its role in processing the cognitive and emotional aspects of pain.

Combining information from this study with previous data, we can now construct a more detailed picture of visceral pain transmission and subsequent cortical processing, showing that the central processing of somatic and visceral pain is similar. Visceral nociceptive signals are transmitted via primary afferents to the spinothalamic tract and postsynaptic dorsal column pathway.50 Here this relatively small afferent input converges with visceral somatic afferents31 and is conveyed to several thalamic nuclei and onto cortical structures. Divergence of the esophageal primary afferents results in the visceral signal entering the spinal cord at several dermatomal levels (C2 to T12),52 and this explains the diffuse nature of the sensation evoked by esophageal stimulation across the chest wall. In addition, rather than projecting specifically to contralateral S1, as seen with noxious stimulation applied to a limb, esophageal representation is diffuse and encompasses bilateral activation of S1 in the trunk and intra-abdominal regions. Simultaneously, as seen in somatic pain,53 activity occurs bilaterally in the operculainsular cortex. After this, activity is also seen in the other major regions of the pain matrix, namely, the cingulate and anterior insula cortex. Early activity in S1, S2, and posterior insula most likely relates to direct projections from the thalamus; however, it is not clear whether the later activity seen in cingulate and anterior insula relates to direct projection from other thalamic nuclei or to secondary processing via intracortical pathways.

This sequence of neural events relates to the early processing of the perceived exogenous component of, in this case, experimentally induced, brief esophageal pain. It is clear that the subsequent processing of such information with regard to attention, emotion, behavioral responses, and modulation involves a much more complex interaction of cortical and subcortical networks, and defects in these endogenous responses to visceral pain may play an important role in the production and maintenance of symptoms in FGD.54 One of the limitations of this study is that the experimental paradigm used is not ideal for the study of this later stage of visceral pain processing. In addition, the ability of MEG to detect deep subcortical structures, which may contribute to abnormalities in the descending control of pain, is currently unproven, and other imaging modalities may be more suitable for such studies. However, the advantage of this approach will be in the differentiation between
primary aberrant mechanisms of visceral hypersensitivity in a heterogeneous FGD population. Specifically, the ability to separate exogenous and endogenous components of pain processing may be the only way to objectively determine afferent pathway sensitivity. This process will be fundamental when considering appropriate administration of antihyperalgesic/analgescic treatments to attenuate visceral hypersensitivity in the future. Also, the fact that this can be achieved with an inexpensive, readily available technique such as CEP means that such studies can be performed on a larger and more cost-effective scale when compared with other brain-imaging modalities.

In summary, we have shown that processing of the early phases of esophageal pain shares many similarities to that seen during somatic pain. We did not observe any sex differences in the psychophysical or neurophysiological responses to painful electrical stimulation of the esophagus with this type of experimental design. Finally, CEP and MEG are currently the optimal methods for unequivocal assessment of exogenous, stimulus-related cortical processing, a fact that will be important to consider when differentiating between primary mechanisms of visceral hypersensitivity in a heterogeneous population of FGD patients.

References

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Address requests for reprints to: Anthony R. Hobson, PhD, Section of GI Sciences, University of Manchester, Clinical Sciences Building, Hope Hospital, Salford, M6 8HD, United Kingdom. e-mail: anthony.hobson@manchester.ac.uk; fax: (44) 161 206 1495.
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