Right-Lateralized Pain Processing in the Human Cortex: An fMRI Study

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Submitted 2 November 2005; accepted in final form 3 March 2006

Symonds, Laura L., Nakia S. Gordon, Jonathan C. Bixby, and Margaret M. Mande. Right-lateralized pain processing in the human cortex: an fMRI study. J Neurophysiol 95: 3823–3830, 2006; doi:10.1152/jn.01162.2005. Neuroimaging studies of human pain have revealed a widespread “pain matrix” distributed across both hemispheres of the brain. It is not resolved whether the pain matrix is biased toward one hemisphere, although behavioral and clinical data suggest that pain is perceived differently on the two sides of the body, and several neuroimaging studies suggest that pain processing in some regions of cortex may be lateralized toward the right hemisphere. The current study used fMRI in nine subjects to determine whether acute pain is preferentially processed in one cortical hemisphere. All cortical areas that were activated during the painful stimulation were investigated, and several analytic approaches were used to directly compare activated regions to similar regions in the opposite hemisphere. Results indicated that four regions of the cortical pain matrix were activated either contralaterally (somatosensory cortex) or bilaterally (mid/posterior insula, anterior insula, and posterior cingulate). In addition, activation in five cortical regions during acute pain stimulation was localized either exclusively in the right hemisphere or was strongly lateralized to the right. These five areas were in the middle frontal gyrus, anterior cingulate, inferior frontal gyrus, medial/superior frontal gyri, and inferior parietal lobule. The location of some of these regions is consistent with the idea that there may be a right-lateralized attentional system to alert an organism to an infrequent, but behaviorally relevant, stimulus such as pain.

INTRODUCTION

Neuroimaging studies of human pain have revealed a widespread “pain matrix” distributed in cortex across both hemispheres (Casey et al. 1999; Davis 2000; Ingvar et al. 1999; Peyron et al. 2000). However, behavioral and clinical studies have demonstrated that on the left side of the body the pain threshold is lower and the perception of pain intensity is higher than that on the right (e.g., Lugo et al. 2002; Pauli et al. 1999; Sarlani et al. 2003; Spernal et al. 2003). This raises the possibility that the right hemisphere plays a dominant role in pain processing. In partial support of this, neuroimaging studies with chronic pain patients who have pain confined to one side of the body have shown that the right anterior cingulate region, but not the left, is active during pain, regardless of the side of the body where pain occurs (Hsieh et al. 1995, 1996).

The issue of whether the pain matrix is biased or “lateralized” to one hemisphere, however, has not been resolved, although evidence from several neuroimaging studies suggests that in some regions of cortex there may be a bias toward the right hemisphere. Four positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) studies have specifically investigated the hemispheric lateralization of pain processing in subjects who were stimulated independently on both the left and right sides. In a PET study using painful thermal stimuli delivered to the right or left forearm, Coghill et al. (2001) identified three separate cortical regions in which activity was restricted to the right hemisphere. According to these authors, these regions, in the inferior parietal lobule (BA40), the dorsolateral prefrontal cortex (BA9/46), and the dorsal frontal cortex (BA6), are active during noxious stimulation, but are also active during nonpainful thermal stimulation and are not sensitive to the intensity of the thermal stimulus. Brooks et al. (2002) anatomically defined four regions of interest in both the left and right insular and cingulate gyrus and used fMRI BOLD (blood oxygenation level dependent) signal to identify which regions were significantly active during painful thermal stimulation of the left or right hand when subjects either attended to the pain or were distracted by a visual-discrimination task. Of the four regions, right-lateralized activity was noted in the anterior insula when pain was attended to, and in a portion of the anterior cingulate regardless of attentional focus. Bingel et al. (2003) and Youell et al. (2004) both used painful laser stimuli and investigated possible laterality biases in three or a priori cortical regions of interest (SI, SII, and insula; in the Bingel et al. study, also a portion of the cingulate gyrus) and reported that each of the regions was bilaterally active during stimulation of either the left or right hand or lower leg.

The current study was designed to further elaborate on whether pain is preferentially processed in one cortical hemisphere by using a rigorous design in which each subject’s 1) physical intensity of the painful stimulus applied to the left and right sides was equal, and 2) perceived intensity of the stimulus applied to the two sides was equal. In addition, because we are interested in the hemispheric distribution of the entire pain matrix, we investigated all cortical areas activated by painful stimuli, regardless of which side of the body was stimulated or in which hemisphere they appeared. We then used several methods to analyze and directly compare each of them to similar regions in the opposite hemisphere.

METHODS

Subjects

Nine right-handed volunteers (six men, three women), ages 22–29 yr (mean 25.5 yr, SD 2.3), with no history of substance abuse, major mental or emotional difficulties, loss of consciousness, migraine, or brain injury, participated in the study. Handedness was evaluated...
using the Edinburgh Handedness Inventory (Oldfield 1971). Women were scheduled for day 18 or more of their menstrual cycle to avoid giving painful stimuli during the periovulatory phase (days 12–16) when electrical stimulation of the skin is reported to result in lower pain thresholds (Giamberardino et al. 1997). Subjects provided written informed consent before experimental procedures and were free to withdraw from the study at any time. All procedures were approved by Michigan State University’s institutional review board.

Experimental procedures

PAIN STIMULATION AND RATINGS. Acute electrical pain stimulation selective for small-diameter pain fibers was applied using a 9-V battery-powered, transcutaneous neurostimulator (Neurometer CPT; Neurotron, Baltimore, MD). The neurometer is capable of producing AC stimuli at frequencies of 5, 250, and 2,000 Hz and has been shown in both animal and human studies to selectively stimulate the small, unmyelinated C; the small, myelinated Aδ; and the large, myelinated Aβ nerve fibers, respectively (Baron and Irving 2002; Dotson 1997; Katims 1998; Kiso et al. 2001; Liu et al. 1995). Selective activation of the C fibers is achieved both because the small-diameter C fibers require several milliseconds of continuous depolarization to respond (rendering only the 5-Hz stimulus effective) and because the larger-diameter Aδ and Aβ fibers depolarize faster than the 5-Hz stimulus can depolarize them so they cannot reach their threshold potential (Katims et al. 1998).

Gold-plated electrodes were applied to the medial and lateral surfaces of the second phalanx of the index finger. Our standard procedure for determining sensory perception thresholds, pain thresholds, and a standard “moderate” level of pain for each subject is described below. First, we obtained perception thresholds to accustom the subject to the device and method of stimulation. Second, the pain perception threshold was determined for each subject by delivering 3-s pulses and slowly increasing the current by 0.05 mA until pain was first reported on a numerical rating scale (NRS) for pain intensity (0 = no pain, 100 = worst pain imaginable; these were the same anchors used for the visual analogue scale [VAS] during MR imaging). Third, a series of 3-s pulses was applied, with incremental increases of 0.05 mA, to establish the stimulation intensities necessary for ratings between 5 and 60. At that point stimulus pulses of random current intensities (in the range of intensities that yielded NRS ratings between 5 and 60) were applied until the subject consistently gave the same NRS ratings to the same current intensities. This generally took about 5 min. To equalize pain perception across all subjects, painful stimuli corresponding to a numerical rating of 40 were considered to be “moderate” pain and were used during imaging. Both of these latter two procedures (establishing the pain perception threshold and the stimulus–response curve) were done separately for the left and right index fingers. To ensure that potential laterality differences were not confounded with a lateral bias of pain sensitivity (e.g., increased pain perception on the left as opposed to the right forefinger), subjects were admitted into the study only if they rated painful stimuli that were of equal physical intensity as equally intense on both right and left (equal defined as within 5% on the 100-point numerical rating scale).

EXPERIMENTAL PROTOCOL DURING IMAGING. Subjects were placed in the scanner, and a strip of tape was secured across the forehead to minimize head movement. Subjects’ hands were attached to hand-paddle response units, and a liquid crystal display screen was fit onto the birdcage head coil so that subjects could view both the instructions and a 10-cm VAS. To acclimate subjects to the fMRI environment, a series of 3-s pulses was applied, with painful stimuli set below the subject’s moderate pain rating. After the practice run, two different series of moderate pain stimulation were run, one each side. Order of series was counterbalanced across subjects. Each series was 4.5 min long, divided into alternating 30-s periods of rest and task, beginning and ending with a rest period. Task periods consisted of six 3-s pulses of painful stimulation (3 s on/2 s off). After each 4.5-min series, subjects rated both the intensity of perceived pain and the intensity of experienced emotion during the series. Response buttons were used to move a cursor along a VAS anchored with “no pain” and “worst pain imaginable” for the pain VAS. In addition, subjects rated the extent to which they were experiencing each of eight emotions: happiness, sadness, anxiety, anger, disgust, guilt, fear, and surprise. Anchors on the emotion VAS were “least possible” and “most possible.”

Data acquisition

Scanning was performed on a 3.0 T scanner (GE Horizon Echo-Speed) with standard quadrature and a birdcage RF coil allowing whole brain imaging. One hundred twenty-eight high-resolution spoiled GRASS axial images (TE minimum, TR 20 ms, flip angle 20°, NEX 1, slice thickness 1.5 mm, FOV 24 cm, matrix 256 × 192) were collected to use as an underlay for functional activity maps. Functional images were collected using a gradient-echo echo-planar pulse sequence (TE 25 ms, TR 3,000 ms, flip angle 90°, NEX 1, slice thickness 4 mm, no gaps, FOV 24 cm, matrix 64 × 64, voxel size = 3.75 × 3.75 × 4 mm, 70 images/slice).

Data analysis

All image analyses were performed using the AFNI software package (Cox 1996). In-plane and three-dimensional motion artifacts were corrected, volumetric registration was performed, and time course of the fMRI signal intensity was corrected for low-frequency baseline drifts and normalized to allow signal averaging. A waveform was selected based on the task (i.e., alternating 30-s periods of baseline and painful electrical stimulation) and a deconvolution program was run to determine the lag that best predicted the BOLD signal in cortical regions known to be responsive to painful stimuli.

Functional time-series images were then generated using multiple regression in which the BOLD signal was correlated on a voxel-by-voxel basis with multiple predictors, including the waveform that best predicted the hemodynamic response, a constant to represent the baseline, and the degree of the polynomial in the baseline model. From this analysis, the average per-voxel activation intensity of each stimulus condition, minus the baseline and linear trend, was extracted. These individual data sets were consulted later to confirm that findings from the averaged data set of nine subjects (see following text) were representative of the majority of subjects, and were not unduly influenced by either outliers or a small number of individuals. The data were smoothed using a 3-mm full-width half-maximum Gaussian filter to compensate for intersubject variability and to allow greater power to detect significant differences across conditions when all nine data sets were combined in the analysis. Anatomical and functional image data sets were linearly interpolated to volumes with 1-mm³ voxels, coregistered, and converted to stereotaxic space (Talairach and Tournoux 1988). The β coefficients from the individual subjects’ multiple regression analyses were used as input for a voxel-by-voxel repeated ANOVA to determine significant regions of activation for moderate pain stimulation on the right and left fingers, Regions of interest (ROIs) for further analyses were identified in the following way. First, Monte Carlo simulations (using AlphaSim within AFNI) were performed to determine an appropriate alpha level for the ANOVA. At an individual voxel-detection probability of P = 0.0002, and a minimum cluster size of 12 voxels (1 mm³), the probability of false detection in the entire data set was determined to be 0.01. A mask was created using this threshold level, and a set of clusters was obtained from this mask. The clusters were then used as data-driven ROIs from which we obtained average z-scores across all nine subjects. To obtain the average z-scores of the ROIs, an average data set was created from all subjects’ functional data and a general linear test was run to obtain t and F statistics from which a map of z-scores could then be derived.
HEMISPHERIC LATERALIZATION OF PAIN PROCESSING

The mask of clusters was applied to this z-score map, and the z-scores of all voxels in each cluster were averaged. In addition, mirror-image clusters were created (i.e., the same y- and z-coordinates and the inverse x-coordinate) and these ROIs were applied to the opposite hemisphere and analyzed in the same way.

In this study we explicitly tested the hypothesis that in some regions of cortex the neural processing of pain is lateralized to the right. It was therefore extremely important to avoid falsely concluding that a region in one hemisphere was significantly more active just because the mirror-image region in the other hemisphere did not appear to be active at the applied cutoff level. In other words, it was important not only to use a conservative threshold to ensure clusters accurately reflected functionally active voxels throughout the whole brain, but also to use a less conservative threshold in defined ROIs to ensure all voxels with significant z-scores were identified. The method used in this study to ensure that regions identified as lateralized were significantly more active than their mirror-image counterparts in the other hemisphere is as follows.

To begin, the mean z-score of each data-driven cluster and its mirror image were directly compared to determine whether z-scores were significantly different at an alpha level of 0.05. When a comparison of clusters and their mirror-image counterparts indicated a significant difference and thus a hemispheric bias of signal intensity, two further methods were applied to ensure that clusters of significant activation that were smaller than those in the applied mask did not go undetected. (The mask of a large cluster, when applied to the opposite hemisphere, might not identify significant activity if the majority of voxels in that region were close to baseline activity and only a minority of voxels in the region were significantly above baseline activity.) The first method was to lower the per voxel threshold to \( P = 0.001 \) (from a value of \( P = 0.0002 \)) and create a new mask with new clusters. The average z-score in the new cluster of interest was then obtained. In doing so, significant activation in a particular ROI sometimes could be “uncovered” in a way it could not have been if the probability of false detection was maintained at a per voxel threshold of \( P = 0.0002 \). The second method was to apply the mask of clusters obtained during stimulation of the other finger. For example, when applying the mask obtained from the per voxel threshold of \( P = 0.0002 \) during painful stimulation of the left finger, the region in the right middle frontal gyrus at the confluence of BA9/46/10 did not meet the criteria to be considered significantly active. However, this region was obviously active during stimulation of the right finger with a z-score of 6.3. Therefore before concluding that the right middle frontal gyrus was active only under conditions of ipsilateral stimulation, the mask of the middle frontal gyrus cluster obtained during stimulation of the right finger was applied to the average data set obtained during stimulation of the left finger. Thus a relevant ROI was identified and it was possible to detect significantly active voxels in the right middle frontal gyrus region during stimulation of the left finger at \( z = 4.5 \) and to determine that the identified voxels were not significantly less active than those activated during stimulation of the right finger. This type of analysis enabled us to avoid falsely identifying activity as related to only one hemisphere or to stimulation of only the left or right finger.

RESULTS

Individual pain perception and emotion ratings during imaging

Subjects rated pain intensity equally on the right and left sides during imaging. Actual current intensities varied across subjects from 110 to 240 mA (the intensity needed to produce a VAS rating of 40 before scanning), although perceived pain was uniform across subjects: VAS scores were 44.5 (±1.5 SE) on the right, and 44.6 (±1.3 SE) on the left \( [t(8) = 0.08, P = 0.96] \). In addition, pain ratings before scanning and during scanning were not significantly different \( [F(1,8) = 0.1, P = 0.76] \). Ratings of individual emotions during imaging were all <10% on the VAS, except for happiness, which was rated at 39.3%: anxiety, 9.8; surprise, 5.6; disgust, 5.6; anger, 5.0; sadness, 4.8; fear, 4.1; guilt, 2.8.

General patterns of cortical activation (see Fig. 1)

The expected cortical regions in the pain matrix were activated in response to electrical pain stimulation (see Table 1 for

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**FIG. 1.** General patterns of cortical activation. Significant activity in response to painful stimulation applied separately to left and right index fingers. Numbers indicate regions of interest: 1, somatosensory/posterior insula; 2, mid/posterior insula; 3, anterior insula; 4, posterior cingulate (BA23); 5, middle frontal gyrus (BA9/46); 6, anterior cingulate (BA32); 7, inferior frontal gyrus; 8, medial and superior frontal gyri (BA6/8); 9, inferior parietal lobule/supramarginal gyrus. Top: activation during stimulation of left finger; axial sections from 10 different z-coordinate locations, from top left to bottom right: +48, +40, +34, +28, +24, +15, +13, +6, +4, −1. Bottom: activation during stimulation of right finger; axial sections from same z-coordinate locations as in top. Alpha level for all activations is set at 0.01. All brain images shown with left hemisphere on the left.
peripheral stimulation at z
significant activation in the left hemisphere after ipsilateral stimulation of right finger). Closer inspection also revealed
ulation of left finger; left somatosensory/insula z
in mid/posterior insula and anterior insula during painful stim-
somatosensory cluster, were significantly and bilaterally active
significant activation, each separate from and anterior to the
individual voxels was required to exceed only
this activation was "uncovered" when the signal in the indi-
tralateral hemisphere during left stimulation, covering only 343
small, however, compared with the area covered in the con-
tralateral hemisphere during left stimulation, the vast majority were
in the right hemisphere, again irrespective of whether the right or left finger was stimulated. These regions were the somatosensory cortex/posterior insula, in which activation was primarily contralateral; the mid/posterior insula and the anterior insular regions, for which activation was bilateral; and the posterior cingulate (BA23), which was activated along the midline. Second, there were five cortical regions for which activity was localized either exclusively in the right hemisphere, or was strongly lateralized so that activation was significantly greater in both spatial extent and signal intensity in the right hemisphere, again irrespective of whether the right or left finger was stimulated.

Contralateral or bilateral activation regardless of side stimulated (see Fig. 1)

SOMATOSENSORY CORTEX/POSTERIOR INSULA. Stimulation of either the right or left forefinger produced significant activation primarily in the hemisphere opposite to the site of peripheral stimulation (right somatosensory/insula z = 7.11 during stimulation of left finger; left somatosensory/insula z = 5.60 during stimulation of right finger). Closer inspection also revealed significant activation in the left hemisphere after ipsilateral peripheral stimulation at z = 5.96. (As described in METHODS, this activation was “uncovered” when the signal in the individual voxels was required to exceed only P = 0.001 rather than the P = 0.0002 cutoff.) This region of activation was very small, however, compared with the area covered in the contralateral hemisphere during left stimulation, covering only 343 mm³ for voxels at P = 0.001 compared with 2,016 mm³ for voxels in the right hemisphere at a more conservative P value of 0.0002.

MID/POTTERIOR INSULA AND ANTERIOR INSULA. Two clusters of significant activation, each separate from and anterior to the somatosensory cluster, were significantly and bilaterally active in mid/posterior insula and anterior insula during painful stimulation of either the right or left index finger. Activation in

mid/posterior insula was centered about 6 mm posterior to the anterior commissure, with activation in the anterior insula at 14 mm anterior to it.

POSTERIOR CINGULATE (BA23). During either right or left painful stimulation, activation in the posterior cingulate region equally straddled the two hemispheres in a cluster about 13 mm wide and we therefore considered the activation to be bilaterally distributed. Significant activation during right index finger stimulation was determined by applying the ROI mask for the left stimulation data set, and calculating the mean z-score for the voxels in that applied region of interest and by doing the same with the mask for the right stimulation data set. Moreover, inspection of individual subjects’ multiple regression data confirmed that activation was equally present in both hemispheres.

Right-lateralized activation regardless of side stimulated (see Fig. 1)

MIDDLE FRONTAL GYRUS (BA9/46). A region in the middle frontal gyrus was significantly active in only the right hemisphere during stimulation of either the right or left finger. Even when the identified region of interest in the right-stimulation data set was applied to the data set during left stimulation, the mean z-scores of the voxels did not even approach significance.

ANTERIOR CINGULATE (BA32). Activity in a region of the anterior cingulate centered at 20 mm anterior to the anterior commissure was strongly lateralized to the right hemisphere. Right-side stimulation resulted in activation only in the right hemisphere; however, the region of activation was smaller compared with that seen during left-side stimulation (82 vs. 504 mm³). Although there were some active voxels in the left hemisphere during left-side stimulation, the vast majority were in the right.

INFERIOR FRONTAL GYRUS. Significantly active voxels in the inferior frontal gyrus were located in only the right hemisphere during either right or left peripheral stimulation. The cluster of activation identified during right stimulation occupied nearly 40% more volume than that identified during left stimulation.

TABLE 1. Cortical areas activated during painful stimulation to left and right fingers

<table>
<thead>
<tr>
<th>Region</th>
<th>Left Stimulation</th>
<th>Right Stimulation</th>
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<tr>
<td></td>
<td>L brain</td>
<td>R brain</td>
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<tr>
<td></td>
<td>Z-score</td>
<td>mm³</td>
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<tr>
<td>[1] SII/insula</td>
<td>[3.70] 5.96*</td>
<td>7.11 (48, −15, 14)</td>
</tr>
<tr>
<td>[4] Post cingulate (BA23)</td>
<td>4.19</td>
<td>4.19 (2, −31, 27)</td>
</tr>
<tr>
<td>[5] Mid frontal (BA9/46)</td>
<td>[1.27]*</td>
<td>4.51</td>
</tr>
<tr>
<td>[7] Inferior frontal</td>
<td>[2.84]</td>
<td>5.36 (48, 1, 10)</td>
</tr>
<tr>
<td>[8] Med/sup frontal (BA6,8)</td>
<td>[5.30]</td>
<td>5.15 (1, 18, 49)</td>
</tr>
<tr>
<td>[9] Inferior parietal</td>
<td>[2.81] 3.60*</td>
<td>5.62 (46, −54, 38)</td>
</tr>
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</table>

Activation z-scores for all cortical areas of activation, regardless of whether they were considered to be significantly active. Numbers in braces preceding the region name correspond to number labels in Figure 1. The z-scores in square brackets indicate that the region of interest (ROI) is the mirror image from a significantly active cluster in the other hemisphere. Talairach coordinates of activated regions are in parentheses. ROIs are obtained from: right stimulation data set; left stimulation data set; and * data set at P = 0.001.

MEDIAL AND SUPERIOR FRONTAL GYRI (BA6/8). Activity in the med}al and superior frontal gyri (BA6/8) was lateralized to the right hemisphere during painful stimulation of either the right or left index finger. Activity observed during left-side stimulation was largely located along the midline, with more active voxels in the right hemisphere. In the averaged data set obtained during stimulation on the left it is difficult to determine how far into the left hemisphere the activation extends. However, inspection of individual subjects' data sets revealed that only one of the nine subjects had more active voxels on the left. During right-side stimulation, virtually all significantly active voxels were in the right hemisphere for all subjects.

INFERIOR PARIETAL LOBULE AND SUPRAMARGINAL GYRUS. A large region in the inferior parietal cortex of the right hemisphere constituting over 2,000 mm$^3$ was significantly active during painful stimulation of either finger. During left finger stimulation a very small region of active voxels in the left hemisphere was identified by inspecting the data set at a per voxel probability of $P = 0.001$. This region, although significantly active ($z = 3.6$) is significantly less active than the large contralateral region ($z = 5.6$) and covers only 8% of the area (461 vs. 5,594 mm$^3$). We therefore consider the activation in the inferior parietal region activity to be right lateralized.

**DISCUSSION**

*Results of this study in the context of the current literature*

In the current study, unilateral application of equally intense electric stimuli to the right and left index fingers resulted in a pattern of activation in some cortical regions that appears to be significantly biased toward the right hemisphere. These right-lateralized regions are separate from areas in which activation is generally found to be either contralateral (SII/posterior insula) or bilateral (mid/posterior insula, anterior insula, and posterior cingulate). They are, however, regions in which pain-related activity is often reported and are therefore considered to be part of a “pain matrix.” The contralateral and bilateral activation in somatosensory cortex, insula, and posterior cingulate is consistent with the four other neuroimaging studies that specifically examine lateralization patterns of acute pain stimulation (Bingel et al. 2003; Brooks et al. 2002; Coghill et al. 2001; Youell et al. 2004).

This particular study was undertaken to discover whether there are any cortical regions in which pain processing appeared to be either uniquely located in, or biased to, the right hemisphere. We therefore used a rigorous design in which painful stimuli of equal physical intensity were delivered to subjects who also perceived and rated the stimuli as equally intense. In addition, we used an analytic strategy that would be maximally sensitive to intensity differences between left and right hemispheres. The results indicate that there are five cortical regions for which the signal was located only in the right hemisphere, or for which the signal was both significantly more intense and covered a greater area in the right than that in the left hemisphere. These regions are the anterior cingulate (BA32), the middle frontal gyrus (BA9/46/10), the medial and superior frontal gyri (BA6/8), and regions in the inferior frontal gyrus and inferior parietal lobule. For some of these areas, there are previous reports in the literature of a right-biased activation during pain. However, this is the first study to identify all five of these as right-lateralized regions. Each of these regions is discussed in the following text in the context of other investigators' observations.

ANTERIOR CINGULATE (BA32). Two separate groups of investigators report right-lateralized pain processing in the anterior cingulate region coextensive with our area of activation. In a PET study, eight patients with painful mononeuropathy in either the left or right leg were scanned during their normal pain state and again during pain relief after regional nerve block. Although pain in these patients was accompanied by bilateral activation in several regions including the anterior insula and posterior cingulate (areas we also found to be bilaterally active during acute experimental pain), the authors reported that anterior cingulate activation was strictly right lateralized (Hsieh et al. 1995). In a recent fMRI study Brooks et al. (2002) delivered thermal pain to the thenar eminence of the right and left hand in 18 subjects who were instructed to attend to either the painful stimuli or to a visual discrimination task. Right-lateralized activity was observed in a portion of the anterior cingulate regardless of attentional focus. Two neuroimaging studies that specifically examined the lateralization of pain processing failed to find activation limited to the anterior cingulate in the right hemisphere (Bingel et al. 2003; Coghill et al. 2001). Methodological differences may contribute to the discrepancy with our results. In the Coghill et al. PET study the anterior cingulate region that matches the coordinates of the area of activation in this study was eliminated from further analysis because activation in both hemispheres exceeded the statistical threshold for significance. We chose a slightly different analytical method in which we directly compared the intensity of signal of each activated cluster to a similar region in the other hemisphere regardless of whether both regions met statistical significance criteria. Bingel and colleagues also observed bilateral, and not right-lateralized, activity in a region of the cingulate gyrus; however, the right-lateralized area of activation in our study was $\geq 20$ mm anterior to their bilateral activation, and it is not clear whether their anterior cingulate ROI included this more anterior part of the cingulate gyrus.

MIDDLE FRONTAL GYRUS (BA9/46/10). The current study revealed a region of the middle frontal gyrus in the dorsolateral prefrontal cortex with strictly right lateralized activation. Coghill et al. (2001) also found this region to be significantly active in only the right hemisphere, although they report this area to be responsive not only to pain but also to nonpainful thermal stimulation. Other studies of pain laterality do not include the dorsolateral prefrontal cortex in their ROIs (Bingel et al. 2003; Youell et al. 2004).

MEDIAL AND SUPERIOR FRONTAL GYRI (BA6/8). In this study we observed that a region in the medial frontal lobe was almost entirely lateralized to the right hemisphere in all subjects. Again, Coghill et al. (2001) also observed a right-hemisphere bias close to this region (centered about 10 mm posterior to, but probably overlapping, our region of activation) during noxious and nonnoxious stimulation. The area was not included as a region of interest in other studies of pain laterality.

INFERIOR FRONTAL GYRUS. A region in the inferior frontal gyrus, although active in both hemispheres, was significantly more active in the right hemisphere in our study. Coghill et al. (2001) also noted bilateral activity in this region related to the...
intense and occupied a larger region than that seen in the right hemisphere. For example, in the somatosensory region, an area that was laterally active. For example, in the somatosensory region, an area that was either contralaterally or bilaterally active, did observe a right-hemisphere bias in this region. Although they were not specifically testing the hypothesis that pain processing in cortex is lateralized to one hemisphere, did observe a right-hemisphere bias in this region when attention was directed toward a painful stimulus. In their PET study, subjects who received painful thermal stimulation to the left hand and a different group of subjects who received the painful stimulation to the right hand both revealed activation in only the right inferior frontal gyrus. Finally, Brooks et al. (2002) observed activity in the right inferior frontal gyrus during attended painful stimulation of either the right or left hand, although their region of activation was somewhat lateral and inferior to our identified region.

Inferior parietal lobule. In our study a large region in the inferior parietal lobule was active almost entirely in the right hemisphere after stimulation of either the right or left forefinger. Coghill et al. (2001) also found right-lateralized activity in this region for both innocuous and noxious thermal stimulation. Peyron et al. (1999) described a large region of activation in the same area of the right parietal cortex both for subjects stimulated on the left hand and for those stimulated on the right hand, but only when subjects were paying close attention to the painful stimulus and monitoring the rise and fall of its temperature.

The robustness of right-lateralized pain processing

The extent to which activation during painful stimuli was lateralized to the right hemisphere was surprising, especially because there are few reports that indicate such a right-hemisphere bias. The extent of right-hemisphere bias can be seen even in areas that were either contralaterally or bilaterally active. For example, in the somatosensory region, although the cortical activity was almost entirely contralateral to the finger receiving the painful stimulus, the activity in the right hemisphere during left-side stimulation was both more intense and occupied a larger region than that seen in the left hemisphere during right-side stimulation.

Impact of study design on results

We can be confident that in the averaged group analysis a more intense signal in one hemisphere did not arise from a more intense perception of the stimulus on the left or right side. Subjects were included in this study only if equally intense electric shocks applied to the right and left index fingers were rated as equally painful. This is particularly important in light of behavioral studies that show a heightened perception to pain on the left side of the body compared with the right (e.g., Sarlani et al. 2003).

Two thirds of the subjects in this study were men. If men tend to process pain in a more right-lateralized fashion than do women, our results could have been partially driven by the greater number of men compared with women in this study. Although inspection of individual subjects’ data sets confirmed the right-hemisphere bias, a larger study including equal numbers of men and women would be necessary to determine whether right-lateralized pain processing is more pronounced in men.

One possible explanation for the right-hemisphere–biased pain processing in our right-handed subjects might be that pain on the left forefinger may have been more “novel” and required more neural processing in the contralateral hemisphere. However, pain was perceived by our subjects to be equally intense on the left and right fingers. In addition, for cortical areas in which a right-hemisphere bias was observed, the bias was also observed during painful stimulation of the ipsilateral right finger.

If subjects experienced more negative emotions during the experiment, then activation in the right hemisphere could be more evident. There is some evidence that negative emotions such as sadness are preferentially processed in the right hemisphere, at least for men (Canli et al. 1998; Hall et al. 2004). However, subjects had extensive experience with the stimulus before they participated in the fMRI experiment and did not appear distressed by the painful stimuli delivered during imaging. The similarity of the behavioral pain ratings for individual subjects before and during scanning supports this. In addition, the low VAS ratings of negative emotions during scanning suggest that the strong right lateralization of pain processing seen in this study is unlikely to be influenced by a right-lateralized system of the affective component of pain.

Why might the right hemisphere be more active during pain than the left hemisphere?

Clinical observations of spatial neglect in patients after brain damage have for years revealed that areas within the right hemisphere, particularly regions in and connected to the right parietal lobe, are critical to voluntarily directing visual attention (e.g., Mesulam 1999). Behavioral and neuroimaging studies have, in addition, convincingly demonstrated that attention and pain are related. It seems reasonable therefore to explore whether the strongly right lateralized activation pattern seen in this study is related to activation of the attentional system. Distraction from a painful stimulus results in lower pain perception and decreased activity in some regions of the pain matrix, and often concomitant increased activity in other regions, presumably either those involved in the distracting task or in the modulation of pain perception (Bantick et al. 2002; Frankenstein et al. 2001; Lange et al. 2001; Petrovic et al. 2000; Peyron et al. 1999; Valet et al. 2004). In contrast, attention to a painful stimulus results in both increased pain perception (e.g., Miron et al. 1989) and an increase in activity in some areas beyond that seen during nonattended pain (Brooks et al. 2002; Peyron et al. 1999). In a particularly relevant and well-executed study, Peyron and colleagues manipulated subjects’ attention toward or away from painful thermal stimuli and identified a primarily right-sided network consisting of prefrontal and posterior parietal cortical areas that was active only when pain was attended to (Peyron et al. 1999). In our study, the absence of explicit instructions most likely left subjects free to attend to the pain, making it likely that at
least some of the BOLD activity was a result of both pain perception and attention to the pain. Right-lateralized activity in our study might therefore be a result of subjects attending to the painful stimuli.

A growing body of literature in cognitive neuroscience lends more general support to the idea that the right-lateralized cortical regions are related to the attentional aspect of pain. Corbetta and Shulman (2002) and others have begun to identify a right-lateralized system that may specifically serve as an “alerting system.” Although this system is proposed in the context of visual attention, a number of areas thought to participate in such an orienting system overlap with right-lateralized pain areas identified in this and in the Peyron et al. (1999) and Brooks et al. (2002) studies. In particular, three such attention-related areas are located in the medial frontal, inferior frontal, and inferior parietal gyri (Arrington et al. 2000; Braver et al. 2001; Corbetta et al. 2000). In addition, in one study (Downar et al. 2000) the inferior frontal region was found to respond to changes in visual, auditory, and tactile stimuli, suggesting that a portion of the right-lateralized alerting system might serve to alert an organism to any behaviorally relevant stimulus, possibly including a painful one.

In this study we investigated whether pain-related activity in humans is biased toward the right hemisphere. We found that among nine cortical regions that are consistently activated when acute pain is applied separately to the left and right index fingers, activity in five of them is strongly lateralized to the right hemisphere. The locations of areas of activation and the apparent dominance of the right hemisphere in the processing of acute pain are consistent with the existence of a right-lateralized attention system designed to alert an organism to an infrequent but behaviorally relevant stimulus. Further exploration of the “attentional pain matrix” may help to disentangle the specific functions of the various cortical regions in the neural processing of pain.

ACKNOWLEDGMENTS

We are grateful to the Department of Radiology at Michigan State University for use of technical computing support and MR facilities. Medical students D. Bates, J. Goodman, and B. Ludwig participated in many of the fMRI studies, and we are grateful for contributions of time, energy, and intellect.

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GRANTS

This work was supported by National Institute of Mental Health Grant MH-66236 to L. L. Symonds.

REFERENCES


