Brain Activity Associated With Painfully Hot Stimuli Applied to the Upper Limb: A Meta-Analysis

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INTRODUCTION

Pain is a universal, aversive experience. At its most benign state, low levels of pain act as a warning against potential tissue damage. When persistent, pain can be associated with profound levels of disability and psychological comorbidity. The supraspinal processes that subserve the experience of pain are of considerable biological and clinical interest. Functional brain-imaging techniques have provided an opportunity to explore critical issues about the central representation and modulation of pain. This opportunity has been embraced by the scientific community, fostering a substantial body of literature addressing fundamental and applied questions about pain and the brain. The time is now ripe for a second-order appraisal of this literature to provide another layer of interpretation to pain-imaging studies.

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ence of pain have argued against a spatially discrete representation of pain in the brain. In their seminal discussion of the gate control theory, Melzack and Wall [1965] dismissed the concept of a “pain center,” pointing to the thalamus, limbic system, hypothalamus, brain stem reticular formation, parietal cortices, and frontal cortices as components of a network of activity associated with a sensation incorporating discriminative, affective, and cognitive dimensions. Studies over the last decade using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have provided an increasingly sophisticated understanding of the representation of pain in the brain, and have revealed a number of neuroanatomical locations of pain-related activity. A consensus about the core substrates of the pain network is emerging with several reviews contributing significantly to that end [Derbyshire, 2000; Jones et al., 2002; Peyron et al., 2000; Porro, 2003]. Empirical meta-analytic techniques have not yet been applied to the task of collating functional imaging data across pain studies.

The pioneering work of groups from Quebec [Talbot et al., 1991] and Hammersmith [Jones, 1991] delivered the first images of pain-related activity in the human brain. The respective presence and absence of primary somatosensory cortex (S1) activity reported in the two studies contributed to an ongoing debate about the role of S1 in pain processing [Bushnell et al., 1999]. Subsequent studies have continued to produce variations on the distributed pain network, reflecting the multidimensional nature of the experience and differences in experimental parameters.

Despite the range of questions that are addressed by pain-imaging research, many experiments report details of brain activity associated with simple comparisons between noxious and innocuous stimuli. The single most common modality used to identify pain-related activity is thermal stimulation of the skin. Thermal stimulation has both logistical advantages and phenomenological attributes that explain the frequent application of heat for psychophysical and brain-imaging studies. Although outliers exist, the pain stimulus–response function for heat does not differ greatly across healthy volunteers [Gracely et al., 1988; Price et al., 1983]. This consistency of response permits the use of a fixed stimulus intensity that is likely to reliably produce a tolerable level of pain in almost all subjects, although some studies tailor stimuli according to the sensitivity of individual subjects by using psychophysical procedures. The neural substrates of pain and thermal sensations share much in common and juxtaposing brain responses to noxious and innocuous heat stimuli are more likely to identify activity that is confined to the unique elements of the pain experience.

The frequent adoption of thermal stimuli for pain-imaging studies has produced a rich vein of information with considerable potential to reveal the most regularly occurring pain-related activations, and the activation likelihood estimation (ALE) method is particularly suited to the search for the primary neuroanatomical substrates of the pain experience [Turkeltaub et al., 2002]. The objective of this meta-analysis is to review the relevant literature and use quantitative meta-analytic tools to establish the common elements of the supraspinal pain network across functional neuroimaging studies that have applied thermal stimuli to the upper limb.

IELD METHODS

LITERATURE SEARCH AND SELECTION

Successive filters were used to identify articles for inclusion in the ALE analysis. In the first instance MeSH terms (pain and brain mapping) were used with key words (heat or thermal) to identify articles published up to the end of 2003, using a standard search engine (Medline). In total, 86 articles were returned by the search. These articles were reviewed to establish that: (1) the sample included healthy volunteers; (2) heat stimuli were used; (3) in the case of contact thermodes, a contrast between innocuous warm and painfully hot stimuli were reported; (4) heat stimuli delivered with laser did not include a tactile component, or a salient nonpainful control contrast was included in the generation of activation maps; (5) stimuli were confined to either the left or right upper limb in any single contrast; (6) the field of view of the images was not confined to a restricted region of the cortex; and (7) results were reported in Talairach or Montreal Neurological Institute (MNI) coordinates. The search for articles also sought to identify any instances of multiple reports of single data sets across articles, to ensure that only one report of a study contributed to coordinates for meta-analysis. This filtering process yielded 23 articles that incorporated standardized stereotactic coordinates of activations associated with painful thermal stimulation of the left or right arm and hand of healthy volunteers.

CONDITIONS AND EXPERIMENTS

Conditions included innocuous thermal stimulation, the absence of any cutaneous stimulation, and noxious thermal stimulation. Experiments included contrasts that produced activations associated with the experience of pain including noxious versus innocuous thermal stimuli applied with temperature-controlled thermodes and noxious laser stimuli versus the absence of stimulation. Articles fulfilling inclusion criteria could potentially contribute more than one contrast from a single modality if multiple sites or intensities of stimulation were employed. To reduce disproportional impact from some studies only one contrast was used from articles that parametrically manipulated pain intensity. In those instances of multiple pain contrasts, the most intense pain versus innocuous or absent stimulation was chosen. Laterality is important when considering somatosensory experiences and consequently contrasts associated with stimuli to the left and right upper limbs were tabulated separately, allowing for a single study to contribute to both, albeit discrete, data sets.
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Analysis

Descriptive information was extracted from each article including imaging modality, sample size, and pain stimulus attributes. Information about stimulus modality (contact or radiant heat), location (site, side), and duration was collated. The intensity of stimuli was collated by method of derivation (fixed or response dependent). A fixed-intensity paradigm was defined as an experiment that used the same level of stimulation for all subjects. A response-dependent paradigm was defined as an experiment that used different stimuli for each subject, the intensity of stimuli used in each case being determined by a prescanning scaling procedure.

Meta-Analysis

We used the ALE analytic strategy [Turkeltaub et al., 2002] whereby results from all studies were converted to the 3D coordinate system of the Talairach atlas. The space for the analysis was divided into 2 mm × 2 mm × 2 mm voxels and a Gaussian filter of 8 mm full-width half-maximum (FWHM) was used to generate ALE maps, which were thresholded by a permutation test controlling the false discovery rate (FDR) at P < 0.01. A minimum cluster size was not applied. ALE maps were generated for left- and right-side pain-related contrasts. Locations of voxels with peak probabilities within clusters and cluster sizes were identified.

RESULTS

The 23 studies used in the meta-analysis are reported in Table I. They included two publications by a group from Hamburg University who split coordinates of a pain-related contrast across studies and were subsequently coded as a single report [Bingel et al., 2002, 2003]. Sample sizes ranged between 6 and 27 subjects. Most studies explored pain-related brain activity using PET (73%) and contact thermodes (68%). A single study employed hot water baths to stimulate the immersed hand. The ventral surface of the forearm (46%) and the dorsum of the hand (40%) constituted the sites of stimulation in almost equal measure with one instance each of stimulation to the upper arm, palm, and whole of hand (immersion in water bath). Laser stimuli were frequently small (e.g., 5-mm spot) and brief (e.g., 1 ms), whereas contact thermodes varied in area (0.79–9 cm²) and were applied for longer periods that were dictated by the ramp times to achieve and recover from target temperatures. Data on pain intensity was not reported in all articles, and variation in measurement strategies across articles did not allow meaningful comparisons. In all instances, either the rationale for stimulus choice or reports of ratings of sensations associated with stimuli confirmed that the contrast of interest (pain vs. the absence of pain) had been achieved.

Clusters

The 22 studies yielded tabulated coordinates for 14 contrasts involving left-side stimulation and 10 contrasts for right-side stimulation. The ALE analysis of the left side incorporated 249 foci and the right analysis used 170 foci. The labels ascribed to the activation loci by the authors of the studies have been summarized in Table II. The number of clusters and their total volume that resulted from the respective left and right ALE analyses reflected the greater number of studies contributing to the left-side comparison (left clusters = 18, right clusters = 16, total volume left = 14,186 mm³, and total volume right = 13,144 mm³). Table III lists the coordinates for each of the clusters from both analyses. Anatomical labels for the clusters were derived with the Talairach Daemon [Lancaster et al., 2000].

Anterior Cingulate Cortex

All studies included in the analysis reported pain-related activity in the anterior cingulate cortex (ACC). The single largest cluster for pain on the left (PL) had a peak voxel in Brodmann area (BA) 32 (x = −2, y = 10, z = 40), but clearly extended into BA24. The left-side contrast also produced a small, discrete area of activity rostral to the primary ACC cluster that was clearly in the left hemisphere (x = −8, y = 24, z = 30). The location of two clusters for pain on the right (PR) substantially overlapped the primary ACC cluster for PL (see Fig. 1a). The more dorsal of the PR clusters had a peak voxel at the midline, (x = 0, y = 0, z = 46), whereas the slightly smaller, more rostral cluster had a peak voxel in the right hemisphere (x = 4, y = 16, z = 28). The Talairach daemon identified BA24 as the location of the two ACC clusters for PR.

Thalamus

Both PR and PL were associated with bilateral activity in the thalamus. The symmetrical distribution of thalamic activity was reflected in the presence of two discrete foci for PL (x = −8, y = −16, z = 10 and x = 10, y = −20, z = 6). A single thalamic cluster with a peak voxel at (x = 10, y = −12, z = 2) was identified by the PR analysis. Although contiguous via a midline connection, the PR thalamic cluster clearly incorporated contralateral and ipsilateral components (Fig. 2, z = 0). There was considerable concordance between the PR and PL clusters, with the later extending superiorly beyond the common area, and the former having a more substantial inferior extent (Fig. 1f). The PR analysis also resulted in a small, mesial thalamic cluster at (x = −4, y = −6, z = 0).

Central Sulcus and Posterior Parietal Cortex

Activity in the region of S1 was reported in approximately half of the studies. Only one cluster, for the PR analysis, was identified as a prospective candidate for activity in S1 (BA3; x = −38, y = −26, z = 62; Fig. 1g).

Two small clusters, one from each analysis, were located in the inferior parietal lobule (IPL) (BA40) in the right hemisphere (PR, x = 54, y = −42, z = 26; PL, x = 52, y = −30, z = 26; Fig. 1e) with PR activity also in the IPL in the ipsilateral hemisphere. The cluster in question incorporates a more extensive region extending into the lateral sulcus.
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### TABLE I. Details of the samples and experimental procedures employed by the studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Publication</th>
<th>Imaging</th>
<th>n</th>
<th>Stimulus</th>
<th>Site</th>
<th>Side</th>
<th>Size (cm²)</th>
<th>Duration (s)</th>
<th>Intensity</th>
<th>Primary question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adler et al., 1997</td>
<td>PET</td>
<td>9</td>
<td>Contact probe</td>
<td>Forearm</td>
<td>L</td>
<td>NS</td>
<td>180</td>
<td>Fixed</td>
<td>Action of fentanyl</td>
</tr>
<tr>
<td>Becerra et al., 1999</td>
<td>fMRI</td>
<td>6</td>
<td>Contact probe</td>
<td>Hand</td>
<td>L</td>
<td>9.0</td>
<td>29</td>
<td>Fixed</td>
<td>Habituation</td>
</tr>
<tr>
<td>Bingel, 2002, 2003</td>
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<td>14</td>
<td>Laser</td>
<td>Hand</td>
<td>L + R</td>
<td>0.2</td>
<td>0.001</td>
<td>Fixed</td>
<td>Somatotopic representation</td>
</tr>
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<td>Bornhovd et al., 2002</td>
<td>fMRI</td>
<td>9</td>
<td>Laser</td>
<td>Hand</td>
<td>L</td>
<td>0.2</td>
<td>0.001</td>
<td>Fixed</td>
<td>Pain-related intensity coding</td>
</tr>
<tr>
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<td>PET</td>
<td>27</td>
<td>Contact probe</td>
<td>Forearm</td>
<td>L</td>
<td>2.5</td>
<td>5</td>
<td>Fixed</td>
<td>Cold vs. heat pain</td>
</tr>
<tr>
<td>Casey et al., 2001</td>
<td>PET</td>
<td>14</td>
<td>Contact probe</td>
<td>Forearm</td>
<td>L</td>
<td>2.5</td>
<td>5</td>
<td>Fixed</td>
<td>Phasic vs. tonic pain</td>
</tr>
<tr>
<td>Coghill et al., 1999</td>
<td>PET</td>
<td>16</td>
<td>Contact probe</td>
<td>Upper arm</td>
<td>R</td>
<td>0.8</td>
<td>5</td>
<td>Fixed</td>
<td>Pain-related intensity coding</td>
</tr>
<tr>
<td>Coghill et al., 2001</td>
<td>PET</td>
<td>9</td>
<td>Contact probe</td>
<td>Forearm</td>
<td>L + R</td>
<td>0.8</td>
<td>5</td>
<td>Fixed</td>
<td>Hemispheric lateralization</td>
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<tr>
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<td>PET</td>
<td>12</td>
<td>Laser</td>
<td>Hand</td>
<td>R</td>
<td>All hand</td>
<td>0.1</td>
<td>Subject dependent</td>
<td>Pain-related intensity coding</td>
</tr>
<tr>
<td>Derbyshire and Jones, 1998</td>
<td>PET</td>
<td>12</td>
<td>Water bath</td>
<td>Hand</td>
<td>R</td>
<td>2.5</td>
<td>150</td>
<td>Subject dependent</td>
<td>Phasic vs. tonic pain</td>
</tr>
<tr>
<td>Derbyshire et al., 2002</td>
<td>PET</td>
<td>16</td>
<td>Contact probe</td>
<td>Hand</td>
<td>R</td>
<td>12.5</td>
<td>15</td>
<td>Subject dependent</td>
<td>Patients vs. controls</td>
</tr>
<tr>
<td>Jones and Derbyshire, 1997</td>
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<td>6</td>
<td>Contact probe</td>
<td>Hand</td>
<td>R</td>
<td>12.5</td>
<td>15</td>
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<td>Patients vs. controls</td>
</tr>
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<td>Contact probe</td>
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<td>Hyperalgesia</td>
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<td>Laser</td>
<td>Forearm</td>
<td>R</td>
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<td>120</td>
<td>Fixed</td>
<td>Action of fluvoxamine</td>
</tr>
<tr>
<td>Paulson et al., 1998</td>
<td>PET</td>
<td>12</td>
<td>Contact probe</td>
<td>Forearm</td>
<td>L</td>
<td>2.5</td>
<td>5</td>
<td>Fixed</td>
<td>Gender differences</td>
</tr>
<tr>
<td>Remy et al., 2003</td>
<td>fMRI</td>
<td>12</td>
<td>Contact probe</td>
<td>Hand</td>
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<td>9.0</td>
<td>13</td>
<td>Subject dependent</td>
<td>Pain effects on cognition</td>
</tr>
<tr>
<td>Smith et al., 2002</td>
<td>fMRI</td>
<td>8</td>
<td>Contact probe</td>
<td>Hand</td>
<td>L</td>
<td>9.0</td>
<td>11.5</td>
<td>Subject dependent</td>
<td>Depression effects on pain</td>
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<tr>
<td>Svensson et al., 1997</td>
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<td>Laser</td>
<td>Forearm</td>
<td>L</td>
<td>9.0</td>
<td>0.05</td>
<td>Subject dependent</td>
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<td>Contact probe</td>
<td>Forearm</td>
<td>R</td>
<td>0.8</td>
<td>4</td>
<td>Subject dependent</td>
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<td>Tolle et al., 1999</td>
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<td>12</td>
<td>Contact probe</td>
<td>Forearm</td>
<td>R</td>
<td>4×3.1</td>
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<td>Fixed</td>
<td>Pain-related unpleasantness</td>
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<td>Tracey et al., 2000</td>
<td>fMRI</td>
<td>6</td>
<td>Contact probe</td>
<td>Hand</td>
<td>L</td>
<td>5.8</td>
<td>25</td>
<td>Fixed</td>
<td>Cold vs. heat pain</td>
</tr>
<tr>
<td>Xu et al., 1997</td>
<td>PET</td>
<td>6</td>
<td>Laser</td>
<td>Hand</td>
<td>L</td>
<td>9.0</td>
<td>0.06</td>
<td>Fixed</td>
<td>Somatotopic representation</td>
</tr>
</tbody>
</table>

The stimulus duration represents the interval between onset and offset of a single application of heat, and does not necessarily indicate the total time that repeated stimuli were applied during a single PET scan or fMRI epoch. The intensity column indicates the method used to determine stimulus intensity across subjects; fixed refers to the use of a single intensity for all subjects, whereas Subject dependent indicates that the intensity was determined for each subject to achieve a uniform rating of pain.

### Lateral Sulcus

Pain-related activations in the insula and opercula cortices are reported commonly and the studies included in the meta-analysis were consistent with this trend. The distribution of ALE clusters in the region of the lateral sulcus warrant careful description that goes beyond citation of coordinates for peak voxels. This caution is required because several of the clusters near the lateral sulcus have loci in either the insula, frontal operculum, or parietal operculum, but had extensive distributions that incorporated more than one neuroanatomical region. In some instances, clusters extended beyond the most lateral extent of the sulcus to include activity in the premotor area or were contiguous with regions of the posterior parietal cortex.

The distribution of pain-related activity near the lateral sulcus could be summarized as bilateral through the anterior and middle portions and confined to the contralateral side in the most posterior part of the insula and parietal operculum. Generally, PL clusters near the lateral sulcus were of greater spatial extent and more likely to demonstrate symmetry across the midline in the anterior and middle portions of the sulcus. Although less robust, the PR
clusters frequently occupied common voxels with PL clusters or the margins of clusters from the respective analyses were in close proximity.

The peak voxels for each of the clusters in the region of the sulcus (Fig. 2) are reported collectively in Table III under the heading of insula and opercula cortices. Of bilateral PR clusters evident in the anterior/mid-insula cortices (Fig. 2, z = 0), only the contralateral of the two extends laterally into the operculum (Fig. 2, slices z = 0 to z = 8). This contralateral PR cluster overlaps to a degree with a smaller ipsilateral PL, cluster near the juncture of insula and opercula cortices (Fig. 2, z = 4). Although not contiguous, PL clusters in the left hemisphere occupy a similar territory to the contralateral PR cluster. The contralateral PL cluster in the right lateral sulcus is of similar spatial extent and orientation to its PR counterpart, extending into the operculum beyond the fundus of the insula. Although bilateral, pain-related activity in the anterior/middle portion of the lateral sulcus thus has a contralateral predominance.

The pain-related ALE clusters in the posterior portion of the insula were contralateral for both PR and PL. The peak voxels for each of the clusters (PL, x = 38, y = −20, z = 16; PR, x = −50, y = −24, z = 20) are both in the parietal operculum and have substantial lateral extents; however, the most medial portions of both clusters incorporate the fundus of the insula (Fig. 1f, z = 16).

Prefrontal Cortex

The PR analysis was notable for an absence of any clusters in the prefrontal cortex. Two small clusters, both in the right hemisphere, were identified by the PL analysis. These clusters were located in the inferior (BA10; x = 38, y = 46, z = 2) and superior frontal gyri (BA9; x = 28, y = 40, z = 30).

Supplementary Motor Cortex and Premotor Cortex

The PL and PR analyses both resulted in clusters with peak voxels in the right supplementary motor area (Fig. 1g). Other clusters with peak voxels in the premotor area were associated primarily with the PL analysis, although there were small areas of overlap between clusters from the two analyses at the margin of the premotor cortex and the lateral sulcus in each hemisphere (Fig. 1a,b). The axial views of this region clearly demonstrate more robust activity associated with PL (Fig. 2, z = 8). The PL cluster in the right hemisphere is contiguous with voxels in the opercula and insula cortices. The PL analysis also produced clusters in BA6 at (x = 10, y = 6, z = 50) and (x = 26, y = 16, z = 52). The former
of these clusters was in close proximity to the most dorsal extent of a PR cluster with a peak voxel in BA24, whereas the latter seemed unique to the result of the PL analysis.

### Lentiform Nuclei

There was only one cluster from the PR analysis that had a peak voxel in the lentiform nucleus ($x = 24, y = -2, z = 2$); however, common voxels from the two analyses that are located at the margin of the right putamen were from clusters that extended into the nucleus (Fig. 2, $z = 4$). A cluster from the PR comparison in the left hemisphere also extended beyond the insula into the putamen (Fig. 2, $z = 4$).

### Cerebellum

Vermal clusters from the PR ($x = 4, y = -48, z = -14$) and PL ($x = 4, y = -58, z = -12$) analyses had a common area of overlap, but extended in anterior and posterior directions respectively. These two clusters seemed lateralized to the right hemisphere (Fig. 1d). Bilateral clusters in the cerebellar hemispheres were in evidence for both the PR (contralateral, $x = -20, y = -64, z = -26$; ipsilateral, $x = 24, y = -58, z = -22$) and PL (contralateral, $x = 38, y = -52, z = -36$; ipsilateral, $x = -26, y = -56, z = -16$) analyses.

### DISCUSSION

Pain arising from brief, noxious, thermal stimulation is associated with a reproducible network of brain activity. The consistency of activation patterns between left- and right-side stimulation, and by implication across different laboratories and samples, lends weight to the conclusion that the results of the ALE analysis represent an archetypal brain response to brief noxious cutaneous stimulation.

The nature of the pain paradigm explored in this meta-analysis warrants elaboration. The experience of pain is subject to considerable modulation that is dependent upon contextual factors. The early experience of pain reduces the

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**TABLE III. Results of ALE for contrasts between pain and innocuous heat applied to the left or right upper limb**

<table>
<thead>
<tr>
<th>Region</th>
<th>Side</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>ALE</th>
<th>Volume</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>ALE</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cingulate</td>
<td>—</td>
<td>-2</td>
<td>10</td>
<td>40</td>
<td>0.049</td>
<td>3,112</td>
<td>4</td>
<td>16</td>
<td>28</td>
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<td>Insula + opercula</td>
<td>—</td>
<td>-8</td>
<td>24</td>
<td>30</td>
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<td>104</td>
<td>0</td>
<td>0</td>
<td>46</td>
<td>0.030</td>
<td>1,424</td>
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<td>Claustrum</td>
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<td>0.025</td>
<td>224</td>
<td>30</td>
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<td>14</td>
<td>0.022</td>
<td>192</td>
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<tr>
<td>BA13</td>
<td>C</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>-50</td>
<td>-4</td>
<td>6</td>
<td>0.027</td>
<td>2,016</td>
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<tr>
<td>BA13</td>
<td>C</td>
<td>38</td>
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<tr>
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<td>1,904</td>
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<td>-6</td>
<td>0</td>
<td>0.023</td>
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<td>Parietal cortex</td>
<td>BA3</td>
<td>C</td>
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<td>—</td>
<td>—</td>
<td>—</td>
<td>-38</td>
<td>-26</td>
<td>62</td>
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<td>BA40</td>
<td>C</td>
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Coordinates are given in Talairach space; cluster volumes are given in mm³ and activation location is denoted relative to the side of stimulation (l, ipsilateral; c, contralateral) except for loci near the midline.

BA, Brodmann area.
risk of injury by facilitating escape reflexes and more complex behaviors. Ongoing pain after injury can enhance repair by protecting vulnerable tissues in the early course of recovery. Upregulation of pain responses from stimuli to and near injured tissues (hyperalgesia) further facilitates protective postures and behaviors during the tissue-healing phase. Under usual circumstances, ongoing pain and hyperalgesia abate as tissue healing occurs. The biological implications of pain that persists beyond the healing phase are less apparent, and it is little surprise that physical and psychological comorbidities are frequent components of suffering associated with chronic pain.

The meta-analysis reported herein draws on a paradigm that is best described as the early warning function of pain. Individual stimuli and blocks of stimulation were short lived and although frankly painful, were of insufficient intensity to cause tissue damage. Exteroceptive elements of pain arising from application of a heat source include attentional and orientating mechanisms that are informed by sensory/discriminative functions such as stimulus intensity coding and localization. The affective domain of pain, a defining quality of the experience [Merskey and Bogduk, 1994], has been conceptualized as incorporating primary and secondary components [Price, 2000]. The aversive nature of pain, its primary unpleasantness, is an inherent aspect of the sensation that would characterize all the paradigms employed by the studies in the meta-analysis. More elaborate, secondary emotional responses to pain can not be inferred reliably from the experimental strategies used by the studies, but would presumably be muted. The appraisal of familiar sensations in the contrived, highly controlled context of a functional imaging experiment would be less likely to arouse overly negative emotional responses. Constraints on movement consistent with appropriate imaging techniques could produce a relatively unique response set that diverges from transient pain in a natural environment. Withdraw reflexes and conscious escape behaviors that are triggered and motivated by nociceptive and pain processes, respectively, must be suppressed by subjects in imaging experiments. This situation could impact on central processes involved in pain-related motor response selection and execution in a fashion that is idiosyncratic to imaging paradigms. Possible exceptions to this postulate are movements associated with facial expressions that may occur at a rel-

![Brain activation map](image)

**Figure 1.**

Meta-analytic activation map based on all primary studies of painful stimuli applied to either the left (orange voxels) or right upper limb (green) or either limb (red, representing areas of activation common to either side of stimulation, not stimulation of both limbs). a: Midline sagittal section (x = 0) showing a common region of activity in the cingulate motor area (red) and discrete regions for lateralized stimulation more rostrally. b, c: Concor
dant bilateral activation for either stimulation side in premotor cortex. d: Right-side concordant activation in the vermis of the cerebellum for stimulation on either side. e: Discrete regions of activation in the right inferior parietal lobe for left and right stimulation (indicated with red arrow). f: Significant regions of bilateral thalamic activation for both stimulation sides, and contralateral insula/opercula activation. g: Discrete activation in pri
mary sensorimotor cortex for right-side stimulation (indicated with red arrow). Axial slices are orientated with the right hemisphere on the right side. Coordinates are according to the convention of negative x-values to the left of the midline, negative y-values posterior of the anterior commissure, and negative z-values inferior to the anterior commissure.
tively unconscious level during the experience of pain [Craig et al., 2001]. It is clear from this discussion of the multiple facets of pain that the central representation of the experience is likely to occur in a distributed network, as was indeed the case.

Most contrasts employed in this meta-analysis incorporate an innocuous control of like modality. The rationale for this approach is to identify activity that is unique to the experience of pain as opposed to tactile sensation generally. In many respects, this approach is well founded although some reservations persist about the degree to which activations reflect functions that are common across both innocuous and noxious sensory processing. A significant increase in signal from a brain region during painful stimulation does not preclude the possibility that the region is involved in processes common to both pain and other sensory experiences, albeit in an intensity-dependent manner [Coghill et al., 1999]. Consequently, when considering the results of the ALE analysis, it is important to acknowledge that pain-related activity in this context does not translate to a network that is dedicated exclusively to pain perception per se.

The peripheral elements of nociception, including small-diameter primary afferent myelinated Aδ and unmyelinated C fibres, enter the spinal cord through the dorsal root and terminate in laminae I and V [Almeida et al., 2004]. Projections from cells with nociceptive input in the dorsal horn ascend in the contralateral spinothalamic tract. In addition to terminations in the major homeostatic regions of the brainstem, spinothalamic neurons project to nuclei in medial and ventral posterior lateral regions of the thalamus. An anatomical and functional distinction is made frequently between lateral and medial pain pathways that are constituted by the targets of projections from the respective groups of thalamic nuclei [Treede et al., 1999]. The classic termination of the spinothalamic pathway, the primary somatosensory cortex is synonymous with the lateral pain pathway and has been ascribed with sensory/discriminative functions. Mesial structures, most notably the ACC, have mutual connections with the medial dorsal nucleus and are likely to be involved in the affective/motivational component of the pain experience.

The ALE results clearly demonstrate consistent bilateral activations of the thalami for painful stimuli to both the left and right upper limbs. The spatial resolutions of the techniques providing the data for the meta-analysis disallow any inferences about the respective medial/lateral positions of thalamic activations; however, the clusters extend to both the medial and posterior/lateral regions of the thalamus. Anatomical studies and cord lesions or direct stimulation of the thalamus in humans suggest that the spinothalamic pathway is predominantly contralateral to the peripheral elements of nociceptive and thermoafferent modalities.

Axial views are at 4-mm intervals from z = 0. The color scheme and orientation of images is identical to that described in the legend to Figure 1. Bilateral pain-related activity is apparent at the anterior/mid-insula for both sides of stimulation. The clusters at the posterior end of the insula are confined to the contralateral side relative to stimulation. Although not incorporated invariably within a single cluster, the general pattern is of activity spreading beyond the insula into the adjacent operculum. At the anterior end of the lateral sulcus, the lateral extent of activity encompasses the premotor cortex on the surface of the brain. At the posterior end of the sulcus activity extends into the posterior parietal cortex.
Pain-related brain activity was investigated across numerous samples using fMRI (functional magnetic resonance imaging). Previous studies have isolated discrete brain regions that respond to painful stimulation, but the exact nature of these responses and their role in pain processing is still under debate.

The role of the contralateral primary somatosensory cortex (S1) in pain processing has been extensively studied. Several meta-analyses have highlighted the consistent activation of S1 during pain-related tasks. However, the extent of this activation and its contribution to pain processing is not fully understood.

The insula, a critically important area for pain processing, has been shown to be involved in the modulation of pain. The insula is part of a larger network that includes the anterior cingulate cortex (ACC) and the thalamus, which are closely involved in the processing of pain signals.

The ventral and dorsal anterior cingulate cortices (ACC) have been implicated in the processing of pain, with the dorsal ACC being more involved in the cognitive and emotional aspects of pain, and the ventral ACC in the somatosensory aspects.

In summary, the pain-related brain activity is a complex and multifaceted phenomenon involving various brain regions, with S1, insula, ACC, and thalamus playing crucial roles in the processing of pain. Further research is needed to fully understand the mechanisms underlying pain processing and the role of these brain regions in pain experience.
imaging experiments of pain. Both the desire to escape and the inhibition of withdraw may be related to the consistent pain-related activity in elements of the motor network for left and right painful stimulation. The possibility also exists that some of these regions may have a more direct role in sensory processes, a hypothesis that has been entertained for the role of the cerebellum in nociception [Saab and Willis, 2003]. The lack of tangible motor outputs associated with the experience of pain in the scanning environment leaves much in doubt. There would be considerable merit in the design of paradigms that incorporate independent and interacting conditions of pain and movement execution. Evidence from other sources, notably experiments employing transcranial magnetic stimulation [Summers et al., 2004; Svensson et al., 2003], would suggest that there is mutual inhibition of the primary motor and somatosensory cortices during pain and movement, respectively. It seems very likely that this type of interaction would also find expression in other components of the motor and pain networks.

The results of the ALE analysis would suggest that pain-related activity in the inferior parietal lobule (BA40) is confined to the right hemisphere. The posterior parietal cortex has extensive connections with the primary and secondary somatosensory cortices and projects via the insula cortex to a number of limbic structures [Cipolloni and Pandya, 1999]. Behavioral responses in monkeys with ablation of the analogous region (7b) support a role for this cortical area in the perception of intrusion or threat from a noxious stimulus [Dong et al., 1996]. This perceptual process seems dependent on the extensive convergence of afferent input in the region of the posterior parietal cortex. Exteroceptive senses, notably vision, have been strongly implicated in the contribution of the posterior parietal cortex to pain processing.

CONCLUSIONS

This meta-analysis of activations associated with noxious thermal stimuli has identified a widely distributed pain matrix. Many elements of the supraspinal pain network have a contralateral or bilateral distribution that is consistent for stimuli either side of the midline. Some findings have dovetailed neatly with other threads of information, such as the convergence of the pattern of mid-ACC activity and more recent characterizations of the cytoarchitecture of this region. Other findings, such as the robust nature of ipsilateral thalamic activity and widespread activity in the motor network, provide considerable impetus for future explorations of these pain-related phenomena.

REFERENCES


