A Positron Emission Tomographic Study in Spontaneous Migraine

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Background: Functional brain imaging in acute migraine has proved challenging because of the logistic problems associated with an episodic condition. Since the seminal observation of brainstem activation in migraine, there has been only a single case substantiating this finding.

Objective: To test the hypothesis that brainstem activation could be detected in migraine and to refine the anatomic localization with higher-resolution positron emission tomography than previously used.

Design: Using positron emission tomography with radioactive water (H$_{15}$O), we studied acute migraine attacks occurring spontaneously. Five patients underwent imaging in ictal and interictal states, and the differences were analyzed by means of statistical parametric mapping.

Setting: Tertiary referral center.

Patients: Six volunteers with episodic migraine were recruited from advertisements in migraine newsletters. One patient was excluded because of use of preventive medication.

Main Outcome Measure: Brainstem activation during migraine state vs interictal state.

Results: Two patients had a typical migrainous aura before the onset of the headache. All of the attacks studied fulfilled standard diagnostic criteria for migraine. Comparing the migraine scans with interictal scans, there was significant activation in the dorsal pons, lateralized to the left (small volume correction, $P = .003$). Activation was also seen in the right anterior cingulate, posterior cingulate, cerebellum, thalamus, insula, prefrontal cortex, and temporal lobes. There was an area of deactivation in the migraine phase also located in the pons, lateralized to the right.

Conclusions: Our findings provide clear evidence of dorsal pontine activation in migraine and reinforce the view that migraine is a subcortical disorder modulating afferent neural traffic.

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in the visual association cortex and spreading contiguously across the cortical surface, traversing vascular boundaries. It is debatable whether the subject experienced an associated visual aura.10

One of the most significant studies in migraine neuroimaging was that of Wellner and colleagues.11 That study involved 9 subjects with migraine without aura. They were scanned during spontaneous migraine attacks and after treatment with sumatriptan succinate. Interestingly, 3 of the subjects were taking migraine prophylactics (β-blockers). The study demonstrated brainstem activation during the migraine that persisted after sumatriptan administration had relieved the pain. The resolution of the PET camera used was not high enough to identify specific nuclei, but the loci of maximum increase were around the dorsal midbrain and dorsolateral pons. It has been difficult to replicate these findings because of the practical logistic limitations of imaging spontaneous migraine, with only a single case having been reported thus far in the literature.12 Indeed, when acute migraine has been studied by magnetic resonance imaging methods, such as perfusion-weighted13,14 or blood oxygenation level–dependent functional magnetic resonance imaging,15-17 the focus has been on patients with migraine without aura or on cortical changes in patients without aura. These studies have produced fascinating results, although they were not primarily aimed at further exploring the issue of brainstem involvement in migraine.

Evidence of a role of the brainstem in migraine has been accumulating for some time, initially based on laboratory studies.18 Clinical data for the involvement of the brainstem in migraine were provided by Raskin et al.19 A subgroup of 15 patients from a group of 175 was described who had no previous headache history and who developed migraine headaches after the implantation of stimulating electrodes into the periaqueductal gray. This observation was reproduced in another series of patients.20 There have also been case reports of new-onset migraine after hemorrhage from brainstem (pontine) cavernous angiomas.21,22

One aim of this study was to replicate and perhaps refine published findings, taking advantage of the advances in PET scanning and analysis methods. We report activation of the dorsolateral pons in a group of patients studied with PET during a spontaneous attack of migraine.

### PATIENTS

We recruited 6 subjects, 3 with migraine with aura and 3 with migraine without aura as defined by the International Headache Society diagnostic criteria,23 and consistent with the revised criteria.24 All of the subjects were female, with an age range of 30 to 55 years (Table 1). They had a migraine frequency of between 1 and 4 per month. One subject was withdrawn from the study because it emerged that she was taking pizotyline. None of the remaining subjects was taking any migraine preventives or other medications.

The subjects were scanned within 24 hours of onset of migraine and before any abortive medication was used. No abortive medications had been taken within the preceding 48 hours. The subjects were offered sumatriptan treatment after the scans. Posttreatment scans were not incorporated into the study design. Pain-free scans were taken at least 72 hours after a migraine headache. The order of scanning was randomized (ictal vs interictal). Informed consent was obtained from all patients, and the study was approved by the joint Ethics Committee of the National Hospital for Neurology and Neurosurgery (University College London Hospital Trust) and the Institute of Neurology (University College London), London, England.

### PET DATA ACQUISITION AND ANALYSIS

The PET scans were performed with a scanning system (ECAT EXACT HR+; CTI Siemens, Knoxville, Tenn) in 3-dimensional mode with septa retracted. An antecubital vein cannula was used to administer the tracer, 9.5 mCi (350 MBq) of radioactive water (H215O). The activity was infused into subjects during 20 seconds at a rate of 10 mL/min. The data were acquired in one 90-second frame beginning 5 seconds before the peak of the head curve. The interval between scans was 8 minutes. Each session involved 4 scans. Attenuation correction was performed with a transmission scan acquired at the beginning of each study. Images were reconstructed by filtered back-projection into 63 image planes (separation, 2.4 mm) and into a 128 × 128-pixel image matrix (pixel size, 2.1 × 2.1 mm2). Statistical parametric mapping software (SPM99; Wellcome Department of Imaging Neuroscience, London; http://www.fil.ion.ucl.ac.uk/spm) was used for data analysis.

### METHODS

#### PATIENTS

Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>MO</td>
<td>MO</td>
<td>MWA</td>
<td>MWA</td>
<td>MO</td>
</tr>
<tr>
<td>Age, y</td>
<td>45</td>
<td>30</td>
<td>48</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>Nausea</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Photophobia</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Phono phobia</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Worse with movement</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Laterality of headache</td>
<td>Right</td>
<td>Left</td>
<td>Left</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td>Attack frequency, No./mo</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Aura</td>
<td>–</td>
<td>–</td>
<td>Visual distortion, clumsiness</td>
<td>Paresthesia, incoordination</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: MO, migraine without aura; MWA, migraine with aura.
Images were realigned with the first as the reference and then coregistered and spatially normalized into the space defined by the atlas of Talairach and Tournoux. The normalized images were smoothed with a gaussian filter of 10 mm full width at half-maximum, because increasing the smoothness of the data increases the sensitivity of the analysis in a monotonic fashion. Statistical parametric maps were derived with prespecified contrasts, comparing regional cerebral blood flow during headache vs rest. An uncorrected threshold of \(P < .001\) was chosen for tabular and graphical reporting. However, our results survived a small volume correction using a 12-mm-radius sphere at \(P < .05\) centered on the brainstem maxima as reported.

The analysis included data from all 5 subjects. There were 3 right-sided and 2 left-sided attacks. Analysis was performed both with and without taking lateralization of symptoms into account. The first analysis discounted the side of the attack. In the second analysis, the scans of subjects with left-sided attacks were reflected across the midline for a “flipped” analysis. This was then analyzed in a multigroup analysis, along with a spatially transposed version of this second group using a fixed effects model. This enabled us to detect responses that lateralize in relation to symptoms. Our statistical model included the main effect of migraine (present vs absent), time (scans 1 through 4), and the migraine \(\times\) time interaction. This general linear model conforms to an analysis of variance.

RESULTS

Two of the patients had a typical migrainous aura before the onset of the headache. All 5 subjects were scanned within 24 hours of onset of migraine. The mean time from onset to scan was 11 hours. Comparing the scans collected during migraine with those out of the attack showed significant activations in the rostral dorsal pons, lateralized to the left (Figure 1). After small-volume correction, the activation was significant at the cluster level \((P = .003, \text{corrected})\).

Responses were also seen in the right anterior cingulate, posterior cingulate, cerebellum, thalamus, insula, prefrontal cortex, and temporal lobes (Table 2, Figure 2). There was an area of deactivation in the migraine phase also located in the pons, lateralized to the right (primary analysis: coordinates 14, \(-28\), \(-20\), with a \(Z\) score of 5.4 [cluster size, 74 voxels]; after flipping: coordinates 16, \(-28\), \(-19\), with a \(Z\) score of 5.4) (Figure 3). This was an unexpected finding and reached the recommended level of significance for exploratory analysis \((P < .05, \text{corrected})\).

### Table 2. Areas of Activation in Migraine State Compared With Interictal State

<table>
<thead>
<tr>
<th>Region of Activation</th>
<th>Coordinates x, y, z (Talairach and Tournoux)*</th>
<th>Z Score of Peak Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate BA24/32 (right)</td>
<td>4, 30, 19</td>
<td>4.66</td>
</tr>
<tr>
<td>Posterior cingulate BA23</td>
<td>0, –45, 34</td>
<td>Infinite</td>
</tr>
<tr>
<td>Prefrontal cortex BA9/10 (right)</td>
<td>6, 57, 16</td>
<td>7.64</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>12, –67, –15</td>
<td>4.95</td>
</tr>
<tr>
<td>Right</td>
<td>10, –42, –12</td>
<td>5.19</td>
</tr>
<tr>
<td>Thalamus (right)</td>
<td>10, –6, 8</td>
<td>4.82</td>
</tr>
<tr>
<td>Insula (left)</td>
<td>–40, 14, 3</td>
<td>4.10</td>
</tr>
<tr>
<td>Dorsal pons (left)</td>
<td>–4, –28, –20</td>
<td>4.97†</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>–42, 12, –24</td>
<td>5.21</td>
</tr>
<tr>
<td>Right</td>
<td>34, 18, –18</td>
<td>6.19</td>
</tr>
<tr>
<td><strong>Flipped Analysis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior cingulate BA24/32 (right)</td>
<td>2, 28, 20</td>
<td>3.81/3.95</td>
</tr>
<tr>
<td>Posterior cingulate BA23</td>
<td>0, –20, 38</td>
<td>7.64</td>
</tr>
<tr>
<td>Prefrontal cortex BA9/10 (right)</td>
<td>6, 49, 14</td>
<td>5.29</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>10, –64, –14</td>
<td>4.29</td>
</tr>
<tr>
<td>Right</td>
<td>–10, –44, –14</td>
<td>5.09</td>
</tr>
<tr>
<td>Thalamus (left)</td>
<td>–8, –4, 14</td>
<td>3.96</td>
</tr>
<tr>
<td>Insula</td>
<td>44, 12, 0</td>
<td>3.85</td>
</tr>
<tr>
<td>Right</td>
<td>–36, –14, 1</td>
<td>3.92</td>
</tr>
<tr>
<td>Dorsal pons (left)</td>
<td>–2, –28, –22</td>
<td>4.60</td>
</tr>
<tr>
<td>Anterior pons (right)</td>
<td>8, –12, –22</td>
<td>3.53</td>
</tr>
<tr>
<td>Temporal lobe</td>
<td>–40, 12, –24</td>
<td>5.45</td>
</tr>
<tr>
<td>Right</td>
<td>36, 14, –14</td>
<td>5.83</td>
</tr>
</tbody>
</table>

Abbreviation: BA, Brodmann area.

*The coordinates refer to voxels significant at \(P < .001\) (uncorrected).
†Also significant at the cluster level (cluster size, 90 voxels), \(P = .003\) (corrected for multiple comparisons across a 12-mm-radius sphere centered on the brainstem maxima as reported).

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After flipping the images so that, effectively, all of the migraines were on the right side, the area of activation in the left dorsal pons remained. A small area in the right anterior pons was also noted that had not been seen in the first (unflipped) analysis.

Comparison of the flipped and unflipped data to assess for areas that lateralized with side of pain showed activation of the thalamus (Table 2). This was the only area of activation to lateralize with side of pain.

**COMMENT**

These new data supplement and support previous findings of activation of the dorsolateral pons in migraine. In addition, there is activation of other structures involved in various aspects of pain and related processing in the brain. We have observed deactivation in the contralateral pons, a new finding in migraine. Our results are consistent with a view of migraine as primarily a subcortical disorder involving dysfunction in brainstem areas probably involved in the modulation of sensory processing.

The areas of activation in the brain reported herein include regions thought to be involved in the central pain matrix. The anterior cingulate has been the most consistently activated area in pain studies. It is thought to be involved in the affective and evaluative dimension of pain. In particular, the right anterior cingulate was found to be active irrespective of the affected side in a study of patients with acute cluster headache. The posterior cingulate is relatively less frequently activated in response to pain. The insula is also consistently activated in experimental pain studies. It has connections with the limbic system and the autonomic system and is thought to be involved in representing the emotional aspect of pain. The thalamus, which is the relay center for afferent input to the brain and the cerebellum, is less consistently activated in experimental pain studies. The prefrontal cortex is involved in the cognitive emotional processing of pain. Activations in the temporal lobes were also found in the study by Weiller et al, and these were in the auditory association areas.

Other functional imaging studies of migraine have also suggested brainstem involvement. The first of these was the PET study by Weiller and colleagues. A case of a glyceryl trinitrate–triggered migraine also demonstrated brainstem activation, on this occasion in the dorsolateral pons. The dorsolateral pons was also recently shown to be active during a study of patients with chronic migraine.

In a study by Cao and colleagues using blood oxygenation level–dependent functional magnetic resonance imaging, migraine was triggered by a visual stimulus in 12 migraineurs, 10 of whom had migraine with aura. Some of these patients were taking migraine prophylactics. They found increased signal intensities in the red nucleus and substantia nigra before the onset of migraine symptoms in 8 symptomatic subjects. This was followed by occipital cortex signal change. In 7 of these subjects they also found signal increases in other brainstem areas, including dorsolateral pons, basilar pons, pontine tegmentum, medial longitudinal fasciculus, periaqueductal gray, and central midbrain, although it was not clear at what time point and for how long these structures demonstrated signal increases. In contrast, brainstem activation has not been noted in other primary headaches, such as cluster headache. It was also noticeably absent in a PET study where capsaicin was injected into the foreheads of subjects to induce pain. The brainstem activation observed in our study seems relatively specific to migraine.

The area of deactivation was an unexpected finding, not previously reported. It is of interest that it was on the opposite side of the pons from the area activated during the migraine state. It is possible that, as one area of the pons is activated, another region is deactivated. In this regard, it is known that the locus ceruleus, which is in the dorsolateral pons and contains neurons that account for 96% of brain noradrenergic projections, has such a reciprocal contralateral inhibitory effect. Such an effect would be an ideal substrate for the laterality of migraine.

The areas of the brainstem suggested to be involved in migraine, namely the locus ceruleus and dorsal raphe, form part of the antinociceptive network and are involved in cerebrovascular control. The serotonergic and...
noradrenergic systems are also involved in the modulation of cortical activity and attentiveness to environmental stimuli.\textsuperscript{42} This may help to explain the so-called associated symptoms of migraine, such as photophobia and phonophobia. The raphe and dorsolateral pontine tegmentum are thought to be involved in sleep and arousal.\textsuperscript{43,44} Migraineurs often experience changes in levels of arousal during various phases of a migraine attack.\textsuperscript{35}

Our results suggest that some of the areas of activation in the study were lateralized irrespective of the anatomic location of the pain. These included the dorsal pons. The main area that was dependent on the anatomic location of pain was the thalamus. There is evidence that pain processing is lateralized in humans. Hsieh and colleagues\textsuperscript{31,46} demonstrated that the right anterior cingulate is activated irrespective of side of pain. Studies with PET have mainly found bilateral activation of the thalamus.\textsuperscript{37} However, more recently, Bingel and colleagues\textsuperscript{48} demonstrated that the lateral thalamus, but not the medial thalamus, showed a contralaterally biased representation of painful stimuli. The lateral thalamus is thought to be somatotopically organized and therefore is involved in localization and discrimination of stimuli.\textsuperscript{33,35} This is consistent with our finding of contralateral activation of the thalamus after the scans were flipped.

Unfortunately, fewer patients completed the study than we had initially planned; although this does not detract from our positive results, there may be other areas that we have not detected. Unlike previous imaging studies in migraine, our study included subjects with migraine both with and without aura, although the latter group were scanned after the aura had subsided.

In conclusion, our data demonstrate activation of the dorsolateral pons on the left side during acute migraine with associated deactivation of the contralateral pons. Areas of activation such as the anterior cingulate, prefrontal cortex, and insula were seen and are consistent with areas seen during studies involving acute pain. The thalamic activation was found to be lateralized contralateral to the side of pain, which is consistent with known anatomy.

Migraine is likely to be a subcortical disorder of brainstem areas involved in the modulation of sensory processing. Imaging these areas in humans contributes to our understanding of this very common and often disabling primary headache disorder.

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REFERENCES


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