Lornoxicam characteristically modulates cerebral pain-processing in human volunteers: a functional magnetic resonance imaging study

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Background. Lornoxicam like other non-steroidal anti-inflammatory drugs (NSAIDs) is widely used for postoperative pain therapy. Evaluation of the effect of lornoxicam on cerebral processing of surgical pain was thus the aim of the present functional magnetic resonance imaging (fMRI) study.

Methods. An fMRI-compatible pain model that mimics surgical pain was used to induce pain rated 4–5 on a visual analogue scale (VAS) at the anterior margin of the right tibia in volunteers (n=22) after i.v. administration of saline (n=11) or lornoxicam (0.1 mg kg⁻¹) (n=11).

Results. Lornoxicam, which significantly reduced pain sensation [VAS: mean (SD) 4.6 (0.7) vs 1.2 (1.5)], completely suppressed pain-induced activation in the SII/operculum, anterior cingulate cortex, insula, parietal (inferior), prefrontal (inferior, medial), temporal (inferior, medial/superior) lobe, cerebellum, and contralateral (e.g. left-sided) postcentral gyrus (SI). Only the hippocampus and the contralateral superior parietal lobe (BA 7) were activated.

Conclusions. As compared with saline, lornoxicam typically suppressed pain-induced brain activation in all regions except the hippocampus. Furthermore, de novo activation was found in the contralateral, superior parietal lobe (BA 7).

Keywords: brain, magnetic resonance imaging; brain, metabolism; brain, oxygen consumption; pain, experimental

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male volunteers \( n=22 \); ASA physical status I) with no history of any drug or alcohol abuse were enrolled.

**Experimental protocol**

Mechanical pressure pain was induced by means of a pneumatic thumper (contact area 1.2 cm\(^2\)) fixed to the anterior margin of the right tibia at 5 cm above the ankle.\(^4\) On the day before fMRI, the pressure needed to provoke pain rated ‘4–5’ on a visual analogue scale (VAS) (e.g. ‘0’ no pain; ‘10’ intolerable pain) was determined in each individual and the application site was marked. The following day the volunteers were randomly (according to randomization list generated by SPSS\(^®\) 14.0 for Windows XP Professional\(^®\) generated) given in a blinded manner either saline \( n=11 \) or lornoxicam \((0.1 \text{ mg kg}^{-1}) \ n=11\) i.v. A latency period of 30 min elapsed before starting the computer-based pain stimulation protocol, which triggered the fMRI measurements.\(^4\) In detail, 30 measurements with painful stimulus followed 30 measurements without paradigm. Mechanical pressure pain lasted 12 s with only the last 5 s being covered by fMRI. A rest interval of 3 s was allowed between two consecutive painful stimuli.

Immediately after the end of fMRI measurement, pain sensation was rated on a VAS.

**Image acquisition**

A whole-body 1.5 T MR Scanner (Magnetom Vision, Siemens, Erlangen, Germany) with a circular polarized head coil (diameter ~25 cm) was used. Functional MR images were collected using a single-shot echoplanar imaging (EPI) sequence with an echo time (TE) of 64 ms, a flip of angle 90\(^\circ\), a matrix of 128×64 pixels, and a field of view (FoV) of 220 mm. For each fMRI session, 40 slices (slice thickness 3 mm; interslice gap 0.75 mm; pixel size 1.72×3.44×3.75 mm; acquisition time 5 s) covered the whole brain and were acquired parallel to the intercommisural line. Anatomic images were acquired as a set of 110 contiguous sagittal slices using T1-weighted 3D-MPRAGE sequences with the following parameters: repetition time 9.7 ms, TE 4 ms, slice thickness 1.5 mm, matrix size 256×256, FoV 230 mm; pixel size 0.9×0.9×1.5 mm.

**Image processing**

Data were processed using statistical parametric mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK). After discharging the first two volumes of each rest and pain period, scans of each individual were realigned to the first scan, subsequently coregistered to the anatomic images, and spatially normalized and resliced to a voxel size of 2×2×2 mm.\(^5\) For group analysis, images were smoothed with a Gaussian kernel filter of 8 mm full-width at half maximum in \( x, y, z \) axes.\(^5\) A fixed-effects model was estimated for the individual participants. The onset vectors of the conditions were convolved with the canonical form of the haemodynamic response function as implemented in SPM2. The significance level was set at \( P<0.05 \) family-wise error corrected for multiple comparisons across the entire brain volume. All images were displayed according to neurological convention. The clusters were localized on the normalized anatomic slices and labelled using Talairach’s nomenclature.\(^6\)

A second-level two sample \( t \)-test was performed to evaluate differences in the activation patterns between the saline and lornoxicam group. The significance level was set at \( P<0.05 \).

**Results**

All volunteers \([n=22; \text{ age: mean (sd) 28 (4) yr; weight: 79 (sd 11) kg; height: 182 (sd 7) cm}]\) completed the study without complication. Technical quality of data was sufficient in all but two volunteers in the lornoxicam group. Pain sensation was rated higher in the saline group [VAS: 4.6 (0.7); pressure: 0.7 (0.3) atm] than in the lornoxicam group [VAS: 1.2 (1.5); pressure: 0.8 (0.3) atm].

**Saline group \( n=11 \)**

Contralateral (e.g. left-sided) activation was found in the postcentral gyrus (SI) and the thalamus (Table 1). All other regions [e.g. SII/operculum, anterior cingulate cortex (ACC), insula, parietal (inferior), prefrontal (inferior, medial), temporal (inferior, medial/superior) lobe, cerebellum, and hippocampus] showed bilateral pain-induced activation (Table 1, Fig. 1).

**Lornoxicam group \( n=9 \)**

Significant activation was found in the contralateral (e.g. left-sided) superior parietal lobe and bilateral in the hippocampus (Table 2, Fig. 2).

**Lornoxicam vs saline (second-level analysis)**

When comparing the results of the saline group with those of the lornoxicam group in a second-level analysis, activation found only in the saline group was located left-sided in the postcentral gyrus (SI) and the thalamus and bilateral in the SII region/operculum, ACC, insula, parietal (inferior), prefrontal (inferior, medial), temporal (inferior, medial/superior) lobe, and cerebellum (Table 3).

In contrast, activation occurring only in the lornoxicam group was located in the left-sided superior parietal lobe (Table 4).

**Discussion**

Lornoxicam de novo activated the contralateral superior parietal lobe but suppressed pain-induced brain activation...
in all regions except the hippocampus as compared with the saline group.

Pain is a purely subjective, unpleasant and emotional experience that is associated with actual or potential injury. The multidimensional (e.g., sensory-discriminative, affective-motivational, and cognitive-evaluative) experience of pain results from the complex interaction of various, distinct brain regions, which as neuronal matrix provide the anatomic-functional basis for pain processing. Locating and analysing the interaction of brain regions involved in pain processing has, in addition to other modalities, increasingly become possible by means of fMRI. It is mainly synaptic activity that appears to cause changes in the regional content of deoxyhaemoglobin, which functions as the intrinsic contrast agent for BOLD-based fMRI. The BOLD signal, however, depends simultaneously not only on the regional cerebral metabolic rate of oxygen consumption but also on the regional cerebral blood flow and regional cerebral blood volume. Therefore, it is of little surprise that direct comparison of fMRI findings with those obtained, for example, with more CBF-dependent methods like positron emission tomography (PET) showed only a 50–85% consistency in the sites, sides and intensities of pain-induced brain activation. Differences in the temporal resolution of fMRI (e.g., seconds) and PET (e.g., minutes) measurements further contribute to their only moderate correspondence. Despite these methodical limitations, a rather complex but increasingly complete picture of central pain processing has emerged. The sensory-discriminative aspects of pain processing are covered by the primary (SI) and secondary (SII) somatic areas, the thalamus and the insular region. Moreover, affective-motivational aspects of pain processing are provided mostly by the cingulate gyrus and insular regions, whereas cognitive-evaluative aspects are ascribed predominantly to prefrontal and parietal cortical regions and to the ACC, this latter triad is also thought to constitute some kind of attentional matrix. Involvement of one region in more than one dimension of pain processing underscores, in general, the complex structure of the neuronal matrix responsible for pain processing. Finally, areas otherwise known to be involved in motor control (e.g., basal ganglia, cerebellum, and supplementary motor area) also exhibit pain-induced activation.

The pattern of pain-induced brain activation varies to some degree as a function of the type of pain (e.g., thermal, electrical, chemical/pharmacological or mechanical) applied. The present study’s mechanical pain is similar to surgical pain insofar as it combines superficial and deep pain qualities. The present study’s activation pattern was contralaterally (e.g., SI, thalamus) but also bilaterally (e.g., SII, insula, ACC, prefrontal, parietal, and temporal lobe) similar to that reported by Creac’h and colleagues in healthy volunteers after applying mechanical pressure pain to the hand. The SI activation found in the present study, however, was confined to BA3, which is thought to represent sensory input from the lower

| Table 1 | Peak coordinates (x, y, z) in Montreal Neurological Institute (MNI) space, cluster size (k), Z and T values for activated brain regions in volunteers (n=11) subjected to mechanical pressure pain to the anterior margin of the right tibia after i.v. administration of saline. Brodmann areas (BA) are given where available. P-values are given for multiple comparisons |
|---|---|---|---|---|---|---|---|---|
| **Anatomic location** | **BA** | **x** | **y** | **z** | **k** | **Z** | **T** | **P-value** |
| Cingulate cortex | Anterior left | 24 | 14 | 26 | 18 | 503 | 7.54 | 10.78 | <0.001 |
| | Anterior Right | 24 | 14 | 38 | 18 | 503 | 7.54 | 10.78 | <0.001 |
| Thalamus | Midline | 24 | 14 | 38 | 18 | 503 | 7.54 | 8.77 | <0.001 |
| Insula | Left | 13 | 14 | 24 | 18 | 503 | 7.54 | 8.77 | <0.001 |
| Parietal lobe | Inferior | 39/40 | 13 | 14 | 26 | 18 | 503 | 7.54 | 8.77 | <0.001 |
| Prefrontal lobe | Inferior | 39/40 | 14 | 14 | 28 | 18 | 503 | 7.54 | 8.77 | <0.001 |
| Temporal lobe | Inferior | 42 | 14 | 26 | 18 | 503 | 7.54 | 8.77 | <0.001 |
| | Right | 42 | 14 | 26 | 18 | 503 | 7.54 | 8.77 | <0.001 |
| Cerebellum | Left | 39/40 | 14 | 14 | 26 | 18 | 503 | 7.54 | 8.77 | <0.001 |
| | Right | 39/40 | 14 | 14 | 26 | 18 | 503 | 7.54 | 8.77 | <0.001 |

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leg. Additionally, bilateral SII and insular activation is consistent with the processing of localization and intensity of nociceptive input.\textsuperscript{13} Whereas the insular involvement in the sensory-discriminative aspects of pain-processing is beyond doubt, its involvement in affective-emotional aspects of pain processing is still only an assumption.\textsuperscript{10} The affective-emotional aspects of the present study’s mechanical pain, however, are evident from the observed cingular activation, as especially the ACC is involved in affective pain processing.\textsuperscript{13} The found activations in the hippocampal formation finally highlight another affective-emotional facet of the present study’s mechanical pain, namely anxiety.\textsuperscript{14}

As mentioned above, the cingulate gyrus, especially the ACC, along with the prefrontal and parietal cortex also constitute a kind of attentional matrix.\textsuperscript{10} In this context, it is of interest to mention the activation observed in the middle/superior temporal lobe (BA 21, 22), which most likely indicates additional audio-semantic (BA 21, 22)\textsuperscript{15} attention. Pain-induced bilateral activation of sensory-integration (e.g. BA 39/40) and motor-control regions (e.g. cerebellum) finally indicates planning and more or less conscious control of presumed withdrawal reactions in our volunteers.

Lornoxicam is a NSAID of the oxicam class with a time-to-peak effect of approximately 20–30 min and an elimination half-time of 3–5 h in healthy young volunteers.\textsuperscript{1} Its well-known efficacy in relieving postoperative pain in humans\textsuperscript{16,17} prompted us to evaluate its effect on cerebral pain processing in an fMRI-compatible model of surgical pain,\textsuperscript{4} whose reliability and reproducibility were

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**Table 2** Peak coordinates \((x, y, z)\) in Montreal Neurological Institute (MNI) space, cluster size \((k)\), \(Z\) and \(T\) values for activated brain regions in volunteers \((n=9)\) subjected to mechanical pressure pain to the anterior margin of the right tibia after i.v. administration of lornoxicam \((0.1 \text{ mg kg}^{-1})\). Brodmann areas (BA) are given where available. \(P\)-values are given for multiple comparisons.

<table>
<thead>
<tr>
<th>Lornoxicam ((n=9))</th>
<th>MNI</th>
<th>Anatomic location</th>
<th>BA</th>
<th>(x)</th>
<th>(y)</th>
<th>(z)</th>
<th>(k)</th>
<th>(Z)</th>
<th>(T)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal lobe</td>
<td>Superior</td>
<td>Left</td>
<td>7</td>
<td>12</td>
<td>64</td>
<td>50</td>
<td>132</td>
<td>5.12</td>
<td>5.15</td>
<td>0.006</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Left</td>
<td>−22</td>
<td>−6</td>
<td>−16</td>
<td>424</td>
<td>6.12</td>
<td>6.17</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>28</td>
<td>−16</td>
<td>−16</td>
<td>91</td>
<td>&gt;7.54</td>
<td>8.21</td>
<td>&lt;0.001</td>
<td></td>
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</tr>
</tbody>
</table>
previously shown. After i.v. administration of lornoxicam, all volunteers reported a significant decrease in pain intensity [VAS: 4.6 (SD 0.7) vs 1.2 (1.5)].

This finding was paralleled by complete suppression of pain-induced activation not only in regions responsible for sensory-discriminative (e.g. SI, SII, thalamus, insula), affective-motivational (e.g. cingulate cortex, insula) or cognitive-evaluative (e.g. prefrontal lobe, parietal lobe, and ACC) aspects of pain-processing but also in the temporal lobe and the cerebellum. Residual activation, in contrast, was present in the hippocampus, whereas de novo activation was found in the contralateral (e.g. left-sided) superior parietal lobe (BA 7).

These findings are consistent with the previously shown existence of a pain-intensity processing matrix, which triggered by pain intensity in a highly interconnected and parallel fashion up- and down-regulates or both brain regions involved in the sensory-discriminative, affective-motivational, and cognitive-evaluative aspects of pain processing. In the present study, the lornoxicam-induced decrease in pain intensity caused a complete suppression of pain-processing areas.

Interestingly enough, a prefrontal cortical region (BA 9) previously shown to be largely independent of pain intensity was found to show no activation when lornoxicam decreased pain intensity. Furthermore, the de novo activation of the contralateral superior parietal lobe (BA 7), which is regarded as a higher sensory-processing area, potentially indicates that the overall quantity of sensory input caused by the used painful stimulus was unchanged. The quality of that sensory input, however, changed insofar as the painful aspect was eliminated by lornoxicam-induced modulation of nociception. The resulting sensory input would still have been sufficient to activate cerebral pain-processing areas, but increased modulatory activity of the BA 7 region potentially suppressed any activation of those pain-processing areas.

The Gray-McNaughton theory proposes that during anxiety the hippocampal formation increases pain by sending amplifying signals to the neural representation of the painful stimulus. Supporting evidence was provided by Ploghaus and colleagues, who showed anxiety when combined with a noxious thermal stimulus to increase activation in the hippocampal formation, the affective-emotional aspects of pain processing ACC and the thermosensitive parts of the insula. Most likely, the volunteers were affected by a certain degree of anxiety, which is defined as apprehension, tension, or uneasiness originating from the anticipation of danger (e.g. painful stimulus). This is supported by the fact that when using lornoxicam and saline we found comparable activation of the hippocampus.

The fact, however, that in the present study anxiety was combined with a lornoxicam-induced decrease in pain intensity [VAS: 4.6 (SD 0.7) vs 1.2 (1.5)]...
level was set at 0.05, it is likely that hypothalamus and hippocampus) are constitutionally (e.g. ubiquitously) and COX 2 (e.g. mainly in the cortex, Cerebellum Left 2).

NSAIDs, lornoxicam inhibits prostaglandin synthesis by inhibiting both cyclo-oxygenase isoforms (COX 1 and 2), but it does not inhibit lipoxygenase activity.21 As COX 1 (e.g. ubiquitously) and COX 2 (e.g. mainly in the cortex, hypothalamus and hippocampus) are constitutionally expressed in the central nervous system,22 it is likely that lornoxicam has not only a peripheral but also a central site of action. Moreover, NSAID-mediated antinociception was previously shown to even use endogenous opioid and serotonin release but also stereotactic NMDA receptor activation.23 The present study’s design, however, does not make it possible to attribute the found lornoxicam-induced changes in cerebral pain processing to solely a peripheral or a central site of drug action.

In conclusion, we here show that lornoxicam in a surgical pain model suppressed pain-induced brain activation in all regions except the hippocampus. Furthermore, de novo activation was found in the contralateral superior parietal lobe (BA 7).

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References
Lornoxicam suppressed pain-induced activation in all regions but the hippocampus


