Positron emission tomography study of a chronic pain patient successfully treated with somatosensory thalamic stimulation

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Abstract

Previous neuroimaging studies suggested that the neuronal network underlying the perception of chronic pain may differ from that underlying acute pain. To further map the neural network associated with chronic pain, we used positron emission tomography (PET) to determine significant regional cerebral blood flow (rCBF) changes in a patient with chronic facial pain. The patient is implanted with a chronic stimulation electrode in the left ventroposterior medial thalamic nucleus with which he can completely suppress his chronic pain. The patient was scanned in the following conditions: before thalamic stimulation (pain, no stimulation), during thalamic stimulation (no pain, stimulation) and after successful thalamic stimulation (no pain, no stimulation). Comparing baseline scans during pain with scans taken after stimulation, when the patient had become pain-free, revealed significant rCBF increases in the prefrontal (Brodmann areas (BA) 9, 10, 11 and 47) and anterior insular cortices, hypothalamus and periaqueductal gray associated with the presence of chronic pain. No significant rCBF changes occurred in thalamus, primary and secondary somatosensory cortex and anterior cingulate cortex, BA 24. Significant rCBF decreases were observed in the substantia nigra/nucleus ruber and in the anterior pulvinar nucleus. During thalamic stimulation, blood flow significantly increased in the amygdala and anterior insular cortex. These data further support that there are important differences in the cerebral processing of acute and chronic pain.

Keywords: Positron emission tomography; Neuropathic pain; Deep brain stimulation; Analgesia; Prefrontal cortex; Anterior insula; Amygdala

1. Introduction

The vast majority of neuroimaging studies of pain processing have focussed on acute, experimentally induced forms of pain. The few studies that investigated chronic pain however do suggest that there are important differences in the cerebral processing of acute and chronic pain (Di Piero et al., 1991; Apkarian et al., 1992; Rosen et al., 1994; Iadarola et al., 1995; Hsieh et al., 1995). To further investigate the neural pathways involved in the processing of chronic pain, we used PET to determine significant changes in rCBF in a 42-year-old man (T.G.) with chronic pain in the right side of the face following injury to the trigeminal nerve. To further investigate the neural pathways involved in the processing of chronic pain, we used PET to determine significant changes in rCBF in a 42-year-old man (T.G.) with chronic pain in the right side of the face following injury to the trigeminal nerve. The study adhered to the guidelines of the Declaration of Helsinki on the use of human subjects in research, and the patient gave written informed consent. A preliminary report has been published in abstract form (Kupers et al., 1998).

2. Materials and methods

2.1. Patient history

In 1989, T.G. had an adenocarcinoma resected from the right cheek. Since this operation, T.G. complained of a sharp, stinging and shooting pain in the right side of the face (V2 area). In addition, he developed hypoesthesia to pinprick and temperature in the affected area. Various surgical and pharmacological treatments (including high doses of morphine up to 540 mg/24 h) were tried but provided no significant pain relief. In 1992, a thalamic stimulation electrode (ITREL III, Medtronic, Minneapolis, MN) was implanted in the left ventroposterior medial thalamic nucleus (VPM). The electrode tip was located 7 mm lateral, 20 mm posterior and 2 mm ventral to the anterior commissure. Thalamic stimulation (10 Hz; pulse width: 0.2 ms, stimulation intensity: 1.7 V) produces tingling and a sensation of warmth in the painful zone. The patient can completely suppress his pain by thalamic stimulation. However, he needs to stimulate permanently to remain pain-free, since...
the original pain reappears several hours after switching off the thalamic stimulator.

2.2. Home evaluation of pain and pain relief

Before the PET study, T.G. was asked for home ratings of his pain in the following conditions: (1) during normal use of the stimulator; (2) following switching-off of the stimulator; (3) following resumed thalamic stimulation after a stimulation-free period of at least 8 h. Pain intensity and pain unpleasantness were measured using a 101-point rating scale ranging from 0 (no pain; not unpleasant) to 100 (most intense/unpleasant pain imaginable). The home ratings were done twice, with a 1-week interval between the two assessment periods. Their purpose was to collect information about the time course of the pain after turning the stimulator on and off. This information was used in the planning of the ensuing PET study.

2.3. PET study

T.G.’s stimulator was switched off the evening before the PET scans to insure a sufficient amount of pain the following day. Cerebral blood flow was measured with an ECAT Exact HR47 PET camera (Siemens/CTI, Knoxville, TN) in 3D mode following bolus injections of 500 MBq of $^{15}$O. A single 60-s frame was acquired, starting at 60 000 true counts/s. Successive scans were separated by at least 12-min. T.G. was scanned in the following conditions: (A) Baseline: scans taken after a stimulation-free period of more than 12 h (pain, no thalamic stimulation); (B) Stimulator on: scans taken while the thalamic stimulator was on (no pain, thalamic stimulation); (C) Stimulator off: scans taken after the stimulator was switched off again (no pain, no thalamic stimulation). Four scans were taken in each condition. The scans were performed in the following order: AA–AA–BB–CC–BB–CC. After every scan, the patient’s pain and the stimulation induced paresthesias were measured using a 101-point rating scale (see above).

The PET images were reconstructed after correction for scatter (Watson et al., 1996) and measured attenuation from a Ga-68 transmission scan. The 47 3.1-mm slices were filtered to 12-mm FWHM isotropic (Hanning filter cutoff frequency 15 cycles/s). PET volumes were realigned using the Automated Image Registration software (AIR) to correct for head movements between the scans (Wood et al., 1992). The first PET image was coregistered with an average MRI volume of 305 normal subjects (Montreal MNI dataset; Collins et al., 1994) and mapped into standardized stereotaxic space (Talairach and Tournoux, 1988) using a nine-parameter affine transformation. $t$-Statistical maps were calculated after a pixel-by-pixel subtraction of PET volumes (Worsley et al., 1992). $P$ values for local maxima were based on the Euler characteristic and calculated according to the method described by Worsley et al. (1996).

3. Results

3.1. Psychophysical data

Fig. 1 shows T.G.’s home pain ratings. The patient is completely pain-free during normal use of the stimulator. When the stimulator is switched off after an extended period of normal use, the original pain reappears 3–4 h later (Fig. 1A). Once the pain is again fully established, 10 min of thalamic stimulation is sufficient to abolish the pain (Fig. 1B). During the PET scans, mean baseline pain intensity and pain unpleasantness were 72.5 ± 5. The patient was pain-free during the stimulator-on and -off scans.

3.2. PET data

Fig. 2A shows $t$-statistic maps of a hemi-comparison of the left and right side of the brain in the baseline (pain) condition. These are obtained by mirroring the PET images and subtracting the mirrored images from the original ones. In this way, a $t$-statistic map of rCBF changes between homologous structures across the midline is created. Although this may pose some problems with cortical structures far away from the midline, for midline structures such as the thalamus, reliable hemi-comparisons can be made.

There was a significantly lower blood flow in the left (i.e. contralateral to the pain) compared to the right thalamus. The left/right ratio of thalamic blood flow was 82.6% vs. 98 ± 3% in a group of eight normal control subjects ($t = 7.8; P < 0.0001$). A left/right asymmetry was also observed in the secondary somatosensory cortex (SII) and in the face region of the primary somatosensory cortex (SI). Fig. 2B shows four transaxial sections through the thalamus.

As can be seen, the asymmetry in thalamic blood flow was highest in the dorsal part of the thalamus (planes 25 and 26). During thalamic stimulation, rCBF in the thalamus increased slightly and the left/right asymmetry in thalamic blood flow was reduced to 85.8% which was still significantly lower than in the control group ($t = 6.3; P < 0.001$). Asymmetry in thalamic rCBF increased again to 80% in the after stimulation condition ($t = 8.5; P < 0.0001$). To test for correlation between left-right asymmetry in blood flow and pain, we performed a second statistical analysis. After factoring out differences in pain intensity, we still observed a significant asymmetry in thalamic blood flow (data not shown), which suggests that the thalamic rCBF asymmetry is independent from the patient’s pain state. Fig. 3 and Table 1 show changes in rCBF estimates for the subtractions ‘baseline (pain) – after stimulation (no stimulation, no pain)’ and ‘stimulator on (stimulation, no pain) – no stimulation (no pain, no stimulation)’. Chronic pain was associated with significant rCBF increases in the prefrontal (BA 9, 10, 11 and 47) and anterior insular cortices, hypothalamus and periaqueductal gray (PAG). Significant rCBF decreases were found in the substantia nigra/nucleus ruber, (supplementary) motor cortex and posterior thalamus.
and/or pulvinar. There were no significant rCBF changes in SI, SII or the BA 240 part of the anterior cingulate cortex (ACC). Thalamic stimulation was associated with significant rCBF increases in the amygdala, the ventromedial frontal cortex and the anterior insula.

4. Discussion

Few PET case report studies on chronic pain have been published. The advantage of single case studies is that the data are not averaged across subjects. As chronic pain patients often vary considerably with respect to the location and etiology of their pain, averaging across a group of pain patients is difficult or arbitrary and may reduce the likelihood of detecting relevant individual rCBF changes. Here we present PET data from a chronic pain patient who was successfully treated with somatosensory thalamic stimulation. The present case is unique in the sense that a completely pain-free state is obtained with thalamic stimulation. In addition, the lingering after-effect of stimulation offers the additional advantage that the chronic pain state and the pain-free state can be compared without the confounding effects of the analgesic procedure (intracerebral thalamic stimulation).

4.1. Methodological considerations

An inherent problem with PET studies of neurostimulation procedures is the timing of the conditions. Because of the long stimulation after-effect, randomization of the scans over time is not possible. Once an analgesic effect is obtained, it may take several hours before the pain returns to baseline levels after switching off the thalamic stimulator (see pyschophysical home ratings). This explains why baseline (pain) scans must be acquired at the beginning of the experimental session. It could therefore be argued that the observed rCBF changes between the pain and pain-free states might reflect monotonic task-independent time effects.
Fig. 2. Hemi-comparison of blood flow in left and right hemispheres in the baseline condition. (A) t-Statistic maps of a hemi-comparison of blood flow in the left and right side of the brain. These maps are created by mirroring the PET images and subtracting the mirrored images from the original ones. A significant increase in rCBF was observed in the right compared to the left thalamus (arrows). (B) Four transaxial slices through the level of the thalamus. The asymmetry in thalamic blood flow was most apparent in the dorsal part of the thalamus (planes 25 and 26).
rather than pain-related changes. For instance, time-related rCBF increases (Rajah et al., 1998) and decreases (Paus et al., 1997) in anterior cingulate cortex have been reported. For the following reasons, we do not believe that the rCBF changes reported here merely reflect task-independent time-related changes. First, while the baseline scans were necessarily done at the beginning of the study, the ‘stimulator on’ and ‘stimulator off’ conditions were randomized. A separate regression analysis on these two conditions, factoring out the effect of stimulation and leaving ‘time’ as single contributor to rCBF changes did not show any significant rCBF changes overlapping with the ones reported in Table 1. In addition, we used a scan timing sequence similar to that of Duncan et al. (1998). Whereas in the present study we obtained a complete analgesia by stimulation, only a mild analgesic effect was obtained in the Duncan study (see below). If the rCBF changes reported here would merely reflect pain-independent time-related changes, they would have been similar to those reported by Duncan et al., which was clearly not the case. Finally, most of the brain areas with alterations in rCBF have been shown to be involved in pain processing (see below). Therefore, the most parsimonious interpretation of the present rCBF changes is that they reflect pain-related changes.

4.2. Chronic pain-related rCBF changes

The present data stand in sharp contrast to the results of functional imaging studies of acute pain. We found no significant rCBF changes in several of the regions normally activated during acute pain, such as the thalamus, primary and secondary somatosensory cortex and BA 24 (Casey and Minoshima, 1997). The lack of activation in the contralateral thalamus and SI/SII region is in agreement with previous reports on chronic pain (Di Piero et al., 1991; Iadarola et al., 1995; Hsieh et al., 1995) and further supports the assumption that areas that are involved in the sensory-discriminative aspects of pain sensation do not play a major role in the processing of chronic pain. It may underscore a major difference in the central processing of acute and chronic pain. An important functional aspect of acute pain processing is to protect the body against sustained tissue injury. Therefore, it is important that the organism has precise information about the localization (and the intensity) of the pain to allow the removal of the afflicted body part from the cause of the pain. This protective function is lacking in chronic pain conditions since there is no external cause of the pain and may explain the absence of activation in these areas. In agreement with earlier reports (Di Piero et al., 1991; Iadarola et al., 1995), we also observed a reduced blood flow in the thalamus contralateral to the painful side in the baseline (pain) scans. In an early SPECT study of patients with cancer-related pain, the reduction of blood flow in the thalamus contralateral to the painful side was abolished after the patients had become pain-free following cervical cordotomy (Di Piero et al., 1991). It was therefore suggested that this reduced thalamic blood flow was at the basis of chronic pain. However, in the present study the

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**Table 1**

<table>
<thead>
<tr>
<th>Region</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t Value</th>
<th>P value (corrected)</th>
</tr>
</thead>
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<tr>
<td><strong>Baseline (pain)—after stimulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbitofrontal cortex (BA 11)</td>
<td>3</td>
<td>47</td>
<td>−22</td>
<td>4.4</td>
<td>&lt;0.005</td>
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<td>Superior frontal gyrus (BA 9)</td>
<td>−21</td>
<td>51</td>
<td>27</td>
<td>4.3</td>
<td>&lt;0.001</td>
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<tr>
<td>Inferior frontal gyrus (BA 47)</td>
<td>−41</td>
<td>37</td>
<td>−3</td>
<td>4.3</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Hypothalamus</td>
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<td>−9</td>
<td>−8</td>
<td>4.1</td>
<td>&lt;0.005</td>
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<tr>
<td>Superior frontal gyrus (BA 10)</td>
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<td>61</td>
<td>−6</td>
<td>3.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Periaqueductal gray</td>
<td>−5</td>
<td>−18</td>
<td>−12</td>
<td>3.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>−33</td>
<td>17</td>
<td>−9</td>
<td>3.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cingulate gyrus (BA 32)</td>
<td>−1</td>
<td>28</td>
<td>−9</td>
<td>3.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Substantia nigra/nucleus ruber</td>
<td>10</td>
<td>−23</td>
<td>−10</td>
<td>−5.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulvinal nucleus</td>
<td>5</td>
<td>−25</td>
<td>18</td>
<td>−3.8</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Supplementary motor cortex (BA 6)</td>
<td>−3</td>
<td>−10</td>
<td>61</td>
<td>−3.7</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Posterior parietal cortex (BA 7)</td>
<td>−9</td>
<td>−36</td>
<td>59</td>
<td>−3.6</td>
<td>&lt;0.01</td>
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<td><strong>Stimulation on—no stimulation</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Amygdala</td>
<td>−25</td>
<td>−9</td>
<td>−15</td>
<td>4.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Anterior insula</td>
<td>−31</td>
<td>15</td>
<td>−6</td>
<td>3.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Ventromedial frontal cortex (BA 25)</td>
<td>8</td>
<td>18</td>
<td>−18</td>
<td>3.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Fig. 3. PET data from ‘baseline – after’ and ‘during – after’ subtractions coregistered with an average MRI volume of 305 normal subjects and mapped in Talairach space. (A) Baseline (pain) compared with stimulator off (no pain). Significant rCBF increases were observed in BA 11 (a), the hypothalamus (b), BA 47 (c) and BA 9 (d). (B) Stimulation on compared with after stimulation (no pain) condition. Significant rCBF increases occurred in the amygdala (a), BA 11/25 (b) and the anterior insula (c).
lowered thalamic rCBF persisted in the pain-free condition, casting doubt on this assumption. In line with the findings by Hsieh et al. (1995) in a group of neuropathic pain patients, we did observe a significantly lower rCBF in the pulvinar nucleus during the chronic pain state. There is evidence for a role of the pulvinar nucleus in pain processing. In cats, pulvinar neurons respond to noxious stimuli (Kudo et al., 1968) and lesions in and electrical stimulation of the pulvinar have been successfully used in the treatment of chronic pain in man (Gybels and Sweet, 1989). Also noteworthy is the significant pain-related reduction in rCBF in the substantia nigra/nucleus ruber. Single unit recordings from dopaminergic nigral neurons in anesthetized rats and awake monkeys have shown that the vast majority of nigral neurons are inhibited by noxious stimulation (Romo and Schultz, 1989). In addition, intranigral injection of morphine produces a naloxone-reversible antinociceptive effect in rats (Baumeister et al., 1987) and electrical stimulation of the substantia nigra suppresses nociceptive responses in the rat parafascicular nucleus (Li et al., 1992).

The most robust activations associated with the chronic pain state were in the prefrontal cortex (BA 9, 10, 11 and 47). Activation of BA 10 or BA 47 was also reported in other studies investigating chronic forms of pain (Rosen et al., 1994; Hsieh et al., 1995; Silverman et al., 1997; Peyron et al., 1998) as well as in capsacain induced allodynia (Iadarola et al., 1998) and in tonic experimental pain (Derbyshire and Jones, 1998). It is unclear what the exact role is of these prefrontal areas in the processing of pain. Fuster (1997) suggested that the ventromedial prefrontal cortex is a depository of emotional memory. In line with this, PET studies have shown that the ventromedial prefrontal cortex is strongly activated by emotional stimuli (Pardo et al., 1993; Lane et al., 1997a,b; Paradiso et al., 1997). Together these data seem to suggest that the ventromedial prefrontal cortex may contain memory traces of the affective component of pain. Previously, Lenz et al. (1995) already showed that pain memory traces could be activated by microstimulation in the thalamic principal somatosensory nucleus.

Chronic neuropathic pain was also associated with significant rCBF increases in the hypothalamus and PAG. These structures are key components of the ‘brain defense system’. Previous PET studies showed hypothalamic and/or PAG rCBF increases during traumatic nociceptive pain (Hsieh et al., 1996), migraine (May et al., 1998) and angina pectoris (Rosen et al., 1994, 1996). There is abundant anatomical and physiological evidence for a role of these areas in pain processing. Direct projections from the spinal cord to the hypothalamus have been described in rats and cats (Burstein et al., 1987; Katter et al., 1991). Single unit recordings in rats showed that a majority of hypothalamic neurons respond to noxious stimuli. In addition, both microiontophoretically applied morphine and direct electrical stimulation of the hypothalamus produce behavioral analgesia in rats (Dafny et al., 1996). In man, hypothalatomy has been used in the treatment of intractable pain (Gybels and Sweet, 1989). The hypothalamus sends afferents to and receives efferents from the orbital and medial prefrontal cortex (Rempel-Clower and Barbas, 1998) and there are reciprocal connections between the hypothalamus and the intralaminar nuclei of the thalamus. It has therefore been suggested that the hypothalamus is involved in the autonomic responses evoked by emotions. It is interesting to note that during the post PET interview, the patient mentioned the occurrence of autonomic responses (sweating, increased heart beat etc.) in response to spontaneous paroxysmal pain attacks in the baseline scans.

The role of the ACC, in particular BA 24', in pain processing, remains an issue of debate. Many studies of acute pain have reported anterior cingulate activation. It has been suggested that the ACC is involved in the processing of pain affect (Rainville et al., 1997). As pain affect rating were high in our study, the absence of activation of BA 24' is surprising. We did, however, observe a rCBF increase in the subgenual part of the cingulate gyrus (BA 32). Chronic and acute pain differ greatly with respect to response inhibition. In contrast to acute pain studies where a noxious stimulus is applied to the skin and subjects are asked to suppress a withdrawal response, there is no external stimulus to withdraw from in chronic pain conditions. Since the ACC also plays a major role in response selection and inhibition (Devinsky et al., 1995), this may explain the lack of activation of BA 24' in chronic pain (but see Hsieh et al., 1994). Although no activation of BA 24' was reported in studies with clinical pain patients (Rosen et al., 1994, 1996; Silverman et al., 1997; Peyron et al., 1998), right BA 24' activation was reported by Hsieh et al. (1995) in patients with neuropathic pain. More studies are needed to figure out the exact role of this area in chronic pain conditions.

4.3. Thalamic stimulation related rCBF changes

Somatosensory thalamic stimulation has been used with varying degrees of success in the treatment of chronic neuropathic pain but not much is known about the mechanisms mediating its analgesic effect (see Gybels and Kupers, 1995, for a review). Although the main purpose of this study was to compare the chronic pain state with the pain-free state after thalamic stimulation, the data also allow us to speculate about the mechanisms mediating stimulation produced analgesia. In a previous PET study on thalamic stimulation, significant increases were found in the thalamus around the stimulation electrode and in the anterior insula (Duncan et al., 1998). The present data partly confirm and extend these findings. During thalamic stimulation we found a subsignificant rCBF increase in the thalamus ipsilateral to the stimulation side. In line with the results by Duncan et al., we also observed a significant rCBF increase in the anterior insula. It is interesting to note that our patient reported a warmth component in his paresthesias, further supporting the hypothesis that somatosensory thalamic stimulation acti-
vates thermal pathways in addition to tactile pathways (Duncan et al., 1998). However, the most conspicuous rCBF increase during thalamic stimulation was found in the amygdala. Activation of the amygdala during thalamic stimulation may be either via direct thalamo-amygdaloid projections or indirectly via the insular cortex. The role of the amygdala in pain processing is well established. Single unit recordings in the rat have shown that neurons in the amygdala are either excited or inhibited by noxious stimuli (Bernard et al., 1996). The amygdala is also involved in opioid analgesia (Helmstetter et al., 1998; Kang et al., 1998) and in stress-mediated analgesia (Helmstetter and Bellgowan, 1993). Unpublished PET data from our laboratory further underscore a role of the amygdala in the processing of experimental tonic and phasic pain. No amygdaloid activation was reported in the study by Duncan et al. (1998)

Major differences of the study design as well as complete pain relief by thalamic stimulation in the present study versus only minor relief in the Duncan et al. study may explain the differences between the results of the two studies.

In conclusion, the present results suggest that chronic pain can be experienced in the absence of activation of the lateral pain system. Our data point to the important role that is played by the prefrontal cortex, the hypothalamus and the periaqueductal gray matter, areas that are strongly implicated in emotion and memory. Although the present data do not allow firm conclusions to be drawn about the mechanisms mediating thalamic stimulation induced analgesia, the strong amygdaloid activation, an area involved both in opioid and conditioned analgesia, is of interest and merits further investigation.

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