PET study on central processing of pain in trigeminal neuropathy

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Recent functional brain imaging studies with positron emission tomography (PET), in painful peripheral mononeuropathy and nitroglycerin-provoked cluster headache attacks, suggest a preference of the right hemisphere, especially the anterior cingulate cortex (ACC) and the medial prefrontal cortex (MPFC), in attributing emotional valence and attention to the pain suffering. We have investigated the central processing of painful trigeminal neuropathy (PTN) in patients treated with electric extradural precentral gyrus stimulation (PCGS). Increased regional cerebral blood flow (rCBF) was detected in the right caudal ACC [Brodmann area (BA) 24] and anterior limbic thalamus, while a decreased activity was observed in the right MPFC (BA 9/32) during the habitual-pain state, in comparison with the pain-alleviated state regardless of the inflicted side of PTN. The involvement of BA 9/32 and the anterior limbic thalamus spatially extended to the left hemisphere, but the local maxima and a significant negative correlation between the rCBF changes in the two structures were found only in the right hemisphere. The activation of the caudal BA24 further supports the theory that ACC is crucial for the suffering in chronic pain. Our study not only verifies the preferential role of the right hemisphere in the appreciation of pain suffering, but further supports that sustained chronic pain, being devoid of the motivational component of an escape response, targets the right hemisphere, particularly the BA24 of the ACC.

INTRODUCTION

Using positron emission tomography (PET) with [15O]butanol, we have previously demonstrated that the activation of the caudal BA24 of the ACC during pain was confined to the right (non-dominant) hemisphere, regardless of the laterality of a painful mononeuropathy in the lower extremities (Hsieh et al., 1995a). The BA24 is an area involved in the emotion-related attention to pain and suffering (Devinsky et al., 1995; Hsieh et al., 1995a). It was further observed that the right hemisphere, especially the BA24 of the ACC and the BA9/32, adjoins the medial prefrontal cortex (MPFC, BA9), and the ACC (BA32), is preferentially engaged in the affective/evaluative processing of the clinical pain syndromes of peripheral mononeuropathy (Hsieh et al., 1995a), and provoked cluster headache (Hsieh et al., 1996b) as well as of anticipation of an impending pain (Hsieh et al., 1999). These observations support our hypothesis that pain devoid of a lateralized motivational component of an escape mechanism (e.g. in experimentally-induced acute somatic pain) preponderantly targets the right hemisphere (Hsieh et al. 1996b, 1999).

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Electrophysiological measures and clinical observations of patients with unilateral frontal lesions have suggested that the right hemisphere is more involved in the mediation of negative affect (Davidson & Hugdahl, 1995). Moreover, experimental and clinical studies have demonstrated that pain sensitivity is lateralized in humans, with the non-dominant hemisphere manifesting a relatively higher response than the dominant hemisphere (Schiff & Gagliese, 1994; Wittling, 1995). Endurance to induced experimental pain has also been reported to be significantly higher in right brain-damaged patients in comparison with both a normal control group and left brain-damaged patients (Cubelli et al., 1984). Furthermore, it has been found that right brain damage affects pain sensitivity both in the contralateral paralyzed arm and in the ipsilateral healthy arm, whereas left brain damage influences the pain sensitivity only in the contralateral paralyzed arm (Neri et al., 1985). In a recent PET study on experimentally induced tonic pain, subjects received bilateral painful cold stimulation on both hands simultaneously and, strikingly, it was only the right ACC (caudal and perigenual cingulate cortex) that was activated (Hsieh et al., 1998).

To further our previous PET findings of a right hemispheric preference in central pain processing (Hsieh et al., 1995a, 1996b, 1999), we in this study investigated another chronic pain syndrome, painful trigeminal neuropathy (PTN). We studied PTN-patients who had been treated with electric precentral gyrus stimulation (PCGS or so-called motor cortex stimulation) for pain relief. PCGS was first introduced by Tsubokawa et al. (1991, 1993), and thereafter developed by Meyerson et al. (1993), to PTN patients with promising analgesic efficacy. The treatment efficacy cannot be ascribed to a placebo effect, since a sham stimulation using a dummy battery under patient-blinded circumstance did not produce any relief from pain. An advantage of PCGS over other forms of therapeutic nervous system stimulation is that it is not accompanied by any subjective sensations during effective analgesic stimulation (Meyerson et al., 1993). This allows a direct assessment of the effects of the stimulation and the central pain-processing with less confounding factors. An attempt to use PET to address possible mechanisms of PCGS in patients with central pain syndrome was recently reported (Peyron et al., 1995, 1998). Since both painful trigeminal neuropathy and cluster headache inflict the trigeminal system, we set out to examine a possible somatotopic organization for emotion-regulated attention for pain in the BA24, similar to a reported somatotopically-organized cognition-directed attention for motor control in the BA32/24 (Paus et al., 1993). In our previous study of cluster headache, we have observed that provoked cluster headache attacks deactivated the left BA24, whilst there was a concomitant activation of BA24 on the right side regardless of the laterality of the cluster headache attack (Hsieh et al., 1996b). A further examination of this reciprocal pattern of activation/deactivation between the BA24 of the two hemispheres was an additional aim of the present study.

**MATERIAL AND METHODS**

**Patients**

The study was approved by the local Ethics and the Radiation Safety committees at the Karolinska Hospital. Informed consent was obtained from all the subjects. We studied five right-handed patients with PTN (right = 2, left = 3) refractory to medical treatment and various surgical interventions, e.g. trigeminal ganglion stimulation, ventroposterior thalamic nucleus stimulation or cervical spinal cord stimulation (Table 1). Before the implementation of PCGS, all of them had episodes of depression and suicidal ideation due to the intractability of the incapacitating disease. This form of trigeminal pain markedly differs from typical trigeminal neuralgia. It is characterized by a continuous, often burning, smarting or aching type of severe and incapacitating pain. The pain is typically aggravated by exposure to wind and cold. The pain is generally located within the trigeminal territory, but it may spread outside this region, involving also the lateral part of the head and the neck. Typically, the patients exhibit prominent changes of sensibility in the painful region.
**TABLE 1. Clinical features of patients with painful trigeminal neuropathy.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Injured nervea</th>
<th>Aetiology</th>
<th>Duration of pain (years)</th>
<th>Sensory signs</th>
<th>Previous surgical treatmentb</th>
<th>PET exam time after PCGS implantation (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL</td>
<td>56/F</td>
<td>I, II, III Lt</td>
<td>surgery/meningioma gun-shot injury</td>
<td>1</td>
<td>anaesthesia</td>
<td>TGS</td>
<td>2</td>
</tr>
<tr>
<td>HV</td>
<td>25/M</td>
<td>I, II Lt</td>
<td></td>
<td>1</td>
<td>hyperalgesia</td>
<td>SCS</td>
<td>2</td>
</tr>
<tr>
<td>MAS</td>
<td>49/F</td>
<td>I, II, III Rt</td>
<td>surgery/parotid tumor</td>
<td>4</td>
<td>allodynia</td>
<td>TGS</td>
<td>45</td>
</tr>
<tr>
<td>NL</td>
<td>46/F</td>
<td>I, II, III Rt</td>
<td>surgery/</td>
<td>21</td>
<td>dysthesia</td>
<td>SCS</td>
<td>1</td>
</tr>
<tr>
<td>YP</td>
<td>48/F</td>
<td>I, II, III Rt</td>
<td>systemic lupus erythematosis</td>
<td>12</td>
<td>dysthesia</td>
<td>SCS</td>
<td>28</td>
</tr>
</tbody>
</table>

*Side of injury: Rt, right; Lt, left; I, ophtalmic; II, maxillary; III, mandibular; C, cervical.

bTGS, trigeminal ganglion stimulation; SCS, cervical spinal cord stimulation.

Hypo- and hyperphenomena often coexist, and allodynia, hyperalgesia and dysesthesia to both mechanical and thermal stimuli are common. These abnormalities may be so severe that the patients are unable to tolerate even the slightest touch of parts of the face. Another characteristic of this form of trigeminal pain is that drugs otherwise effective for trigeminal neuralgia, such as carbamazepine, phenytoin and baclofen are of no avail. Patients with PTN often have a history of injury to the peripheral part of the trigeminal nerve as a result of trauma or surgery or possibly infection.

**Case 1 (BL)**

A 56-year-old woman. In 1986, the patient experienced a moderate and intermittent pain behind the left eye. Progressive sensory loss in the left side of the face was noted. In 1993, a meningioma in the apex of the pars petrosa was demonstrated. A surgical intervention resulted in almost complete loss of sensibility in the entire trigeminal territory. She experienced a new and severe continuous pain having a character of pressure and felt concentrated behind and around the eye. The pain intensity was rated as 70–95/100, using a 100-mm visual analogue scale (VAS). The pain was aggravated by exposure to light. There was no effect of medication including opioids. The patient became severely depressed. PCGS was implanted in October 1993. Stimulation reduced the pain from 70–95 to about 20/100 mm on the VAS, and the post-stimulatory effect lasted for about 3 h.

**Case 2 (HV)**

A 25-year-old man. In 1991, he was a victim of gun-shot injury of the left jaw, which resulted in a severe pain confined to the third trigeminal branch. Extensive reconstruction and plastic operations were performed. Marked hypesthesia and partial anaesthesia combined with hyperalgesia in the adjacent part of the territory of the second branch was noted. Insufficient relief was obtained with high doses of analgesics including opioids. He was subjected to trigeminal ganglion stimulation, instituted via a subtemporal approach to the trigeminal cistern. Moderate pain relief for a few months was achieved, but the pain recurred and became unbearable. Stimulation in the uppermost part of the cervical cord, in order to stimulate the spinal trigeminal tract, was of no avail. PCGS was implanted in 1993. This treatment produced almost complete suppression of pain lasting for 2–4 h following 30 min of stimulation.

**Case 3 (MAS)**

A 49-year-old woman. Right-side trigeminal pain started immediately after surgery for a polymorphic adenoma of the parotid gland. The
operation was uneventful, but for a moderate peripheral facial palsy. The patient developed a marked disturbance of sensibility in the form of allodynia comprising all three trigeminal branches, apart from a limited portion of the lateral territory of the second branch where there was instead a marked hypesthesia. The allodynia was present also on the ear and in the lateral part of the neck. No effect was obtained with various analgesics including opioids. Percutaneous trigeminal ganglion and rootlets stimulation did not produce pain relief, in spite of paresthesia covering the major part of the face. She was then subjected to implantation of an electrode in the upper cervical region, aimed at stimulating the spinal trigeminal tract, and this treatment initially provide some pain relief. PCGS was eventually implanted in 1990, and satisfactory pain relief was achieved for 6 months. Several revisions of the electrode were performed to improve the analgesic efficacy. PCGS for 30–40 min provided almost complete relief for 2–3 h.

**Case 4 (NL)**

A 45-year-old woman. In 1971, the patient was diagnosed as having occipital neuralgia with a progressive onset in the right part of the neck. In 1973, exaeresis of the right occipital nerve was performed with little benefit. Progressive pain radiating within the territory of the supraorbital nerve on the right side was noted. Regional nerve blocks produced temporary pain alleviation. In 1975, an exaeresis of the right supraorbital nerve was performed. Due to continued and aggravated pain, repeated exaereses were performed on the occipital nerve in 1977, and of the supraorbital nerve in 1978. Medication with carbamazepine, analgesics, tricyclic antidepressants or antiepileptic drugs was of no avail. In 1991, she presented with a severe, continuous pain comprising almost the entire right half of the head, and extending down in the upper posterior and lateral parts of the neck with dysesthesia, allodynia and hyperalgesia. Transcutaneous electric nervous stimulation provided short-lasting relief. Stimulation of the trigeminal ganglion and trigeminal rootlets via a temporarily, percutaneously-implanted electrode did not provide adequate pain relief, in spite of the presence of paresthesia, which covered the major part of the painful area in the trigeminal region. PCGS was implanted in 1992. Complete pain relief was achieved with a marked suppression of the cutaneous dysesthesia and allodynia. Thirty minutes of stimulation provided 3–4 h of pain relief.

**Case 5 (YP)**

A 48-year-old woman. Many years' history of systemic lupus erythematosus (SLE). She developed a sudden onset of right-sided trigeminal pain of a continuous type combined with paroxysmal shortlasting pain components in 1978. No aetiology of the pain could be found, despite extensive neuroradiological examinations. Slow progression of sensation of numbness compressing the entire half of the face and spreading down into the right side of the neck was noted. Carbamazepine had a temporary effect on the paroxysmal pain components, whereas the continuous pain was unaffected. Arthrosis of the right mandibular joint was disclosed and the patient was subjected to two operations. Facial and neck pain remained. In 1984, marked hypesthesia to touch in the entire trigeminal territory, as well as the major part of the right half of the head and the neck, was noted. In parts of the trigeminal region, particularly in the territory of the second branch, there was dysthesia and allodynia as well as hyperalgesia. High cervical spinal cord stimulation offered good relief for 6 months, but eventually failed, due to the exacerbation of allodynia and dysesthesia accompanied by a more severe ongoing, as well as evoked pain. PCGS was implanted in 1991. Stimulation produced excellent relief of both ongoing and evoked pain, as well as a marked suppression both of allodynia and dysthesia. PCGS for 30–40 min provides 80% analgesic effect lasting for 6–10 h.

**Surgical procedure**

The surgical procedure has previously been detailed (Meyerson et al., 1993). In short, surgery was performed under local anaesthesia. Somatosensory-evoked responses to median nerve
stimulation were employed to locate the contralateral central sulcus-primary motor cortex, by means of phase-reversal of the N20 wave (Wood et al., 1988). A 4-polar electrode strip (Resume@, Medtronic Inc.) was introduced epidurally through a burr hole contralateral to the diseased side. Local muscle twitches in the contralateral facial or hand regions were induced by low-frequency, high-intensity stimulation, to ensure the proper positioning of the electrode on the motor cortex. After trial stimulation via percutaneous, temporary leads performed during 1–2 weeks, the electrodes were connected to a passive receiver (Xtrel, Medtronic) placed in a subcutaneous pocket below the clavicle. The patients rated their pain suffering (unpleasantness) with a 100-mm visual analogue scales (VAS; anchored with 0 = ‘not at all’ and 100 = ‘the worst imaginable’). The patients discontinued the usage of PCGS after 00:00 h (about one treatment cycle) on the day of the PET examination. PET study commenced at 08:15 h to avoid protracted pain.

PET experimental paradigms

We used [15O]butanol as the tracer for rCBF. The PET scanning (Scanditronix PC-2048-15B) (Holte et al., 1989) of brain tissue radioactivity (100-s uptake image, uptake reflecting rCBF; Ingvar et al., 1994) was commenced simultaneously with the injection of [15O]butanol (half life = 123 s, 27–30 mCi, 62–74 MBq). Subjects’ eyes remained closed during actual scanning and the light was dimmed. Each patient was subjected to nine consecutive rCBF (uptake) studies: [1-3] habitual-pain state, first to the third scan with at least 10 min interval in between; [4-6] during-PCGS treatment (the fourth scan acquired 10 min after the resuming of PCGS, followed by another two studies separated by 10 min); [7-9] pain-alleviated state, obtained 25 min after the discontinuation of stimulation followed by another two studies separated by 10 min. As a pilot study, patient NL (right PTN) was scanned twice during habitual-pain state, once during cortex stimulation and once during pain-alleviated state. Patients rated the unpleasantness of their ongoing pain with a 100-mm VAS.

PET image analysis and statistical treatment

The image analysis and statistical methods have previously been described (Hsieh et al., 1996b; Ingvar et al., 1994). To avoid provocation of alldynia and dysthesia, patients did not wear a head-fixation device during PET examination. All the scans were aligned with respect to the first one of each individual, using the Automated Image Registration software (Woods et al., 1993) to correct for head movements between scans. Images were stereotactically reformatted [2.6 × 2.6 × 2.8 mm, 48 slices, with computerized brain atlas procedure (Greitz et al., 1991), normalised (Ingvar et al., 1994) and filtered with 16 mm FWHM to generate state-dependent omnibus significance maps (p-maps). The filtering was done in-slice, and hence the smoothing was not isotropic. However, this was not expected to influence the results, since statistics were based on the analyses of peak activity. To address the central processing of pain, habitual-pain state (scans 1–3) was compared to the pain-alleviated state (scans 7–9) to generate state-dependent averaged difference and variance images. The rCBF change during PCGS was only analysed for changes underlying the site of stimulation. The p-maps (thresholded at \( p < 0.01 \)) were created by assigning different colours, depending on the \( t \)-value and probability factor of a pixel, and colour-coded into four levels defined by: 0.001 ≤ \( p < 0.01 \) (increase = red; decrease = blue) and \( p < 0.001 \) (increase = yellow; decrease = light blue). The final designation of significant change was based on the calculated local Z-score maximum \( [Z_{\text{max}} \text{ as the centre-of-mass (Friston et al., 1991; Ingvar et al., 1994)}] \). Since the regions of interest (including prefrontal cortex, BA24, BA9/32, thalamus, midbrain, and cerebellum) were selected a priori according to our previous studies (Hsieh et al., 1995a, 1996a, 1996b, 1999), the analysis and discussion were confined to these predefined regions. The study design was within-group comparisons only, and no attempt was made to separately analyse patients with left- or right-sided lesions, because of the limited sample of patients available for this study. Regions of prominent concordant change of activity (increase and decrease) will be preserved.
TABLE 2. Foci of significant changes of rCBF: habitual-pain state vs pain-alleviated state. The changes in all regions listed attained significant levels of \( p < 0.001 \) without correction for multiple comparison. Stereotaxic coordinates of peak activation (Talairach & Tournoux, 1988) are expressed in mm and refer to medial-lateral position (x) relative to midline (positive = right), anterior-posterior position (y) relative to the anterior commissure (positive = anterior), and superior-inferior position (z) relative to the commissural line (positive = superior).

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann area</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ant. cingulate</td>
<td>24</td>
<td>x -16</td>
<td>-8</td>
</tr>
<tr>
<td>Ant. thalamus</td>
<td>3</td>
<td>9</td>
<td>53</td>
</tr>
<tr>
<td>Medial prefrontal</td>
<td>9/32</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>Frontopolar</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle frontal</td>
<td>10/48</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>9</td>
<td>-60</td>
<td></td>
</tr>
</tbody>
</table>

whereas those with discordant, contralateralized or small magnitude of responses will be obscured in the significance maps (Hsieh et al., 1995a, 1996b). Anatomical structures and Brodmann areas [BA; (Brodmann, 1909)] were designated according to the brain database (Greitz et al., 1991). Since the rCBF changes are tightly coupled to the levels of regional neuronal activity (Raitche, 1987), the increase and decrease of rCBF accordingly indicate either an increased or a diminished net regional neuronal activity, respectively, and therefore physiologically and operationally imply a pain-specific (compared to pain-alleviation state), functional activation or deactivation/disengagement of the involved brain regions (Ghatan et al., 1998; Hsieh et al., 1996a; Ingvar & Hsieh, 1999). The rCBF pattern was interpreted in this context. A paired t-test was employed for analysing changes of VAS ratings and the difference of activity in BA24 between the two hemisphere.

RESULTS

The patients did not demonstrate any overt depressive or neurotic traits at the time of the PET study. Nevertheless, pain suffering due to the overnight abstinence from PCGS for pain relief was reported by the patients on the day of the PET examination. The pain ratings before PCGS (habitual-pain state) ranged from 70–98/100 mm (88 ± 11 mm; mean ± SD). Pain suffering dramatically decreased during PCGS and dropped to 2–28/100 mm (11 ± 11 mm) by VAS after PCGS (pain-alleviated state). Thus, on average, a 88 ± 11% reduction of pain (paired t-test, \( p < 0.001 \)) was achieved with PCGS. In all patients, PCGS evoked no subjective sensations, and the patients spontaneously expressed their satisfaction with the pain relief after PCGS.

During pain (habitual-pain state vs pain-alleviated state), markedly increased activity in the right caudal ACC (BA24) and in the right anterior thalamus was noted (Table 2, Fig. 1). Despite the spatially bilateral involvement of the anterior thalamus (Fig. 1), the local maximum was located in the right mediodorsal nucleus according to the stereotactical atlas by Talairach and Tournoux (1988). A concomitant decreased activity in BA9/32 spatially extended to both hemispheres, but the local maximum was located in the right hemisphere. Averaged difference images, left \((n = 2, \text{average of 6 paired subtractions})\) and right \((n = 3, \text{average of 8 paired subtractions})\) PTN, respectively, revealed a right-sided change of activity in these two regions regardless of the painful side (data not shown). While heightened activity in the right BA24 during habitual-pain state decreased during PCGS and pain-alleviated state, a concomitant trend of increased activity in the left BA24 during PCGS and pain-alleviated state was observed. The right BA24 demonstrated a significantly higher activity than the left BA24 at a group level (Fig. 2, habitual-pain state vs pain-alleviated state; paired t-test, \( p < 0.001 \)). This relationship was also seen in the averaged difference images, when the patients were grouped
FIG. 1. Cerebral areas of significant changes in rCBF during the habitual-pain state of PTN. The omnibus significance maps (p-maps) are colour-coded into four levels (uncorrected), defined by $0.001 \leq p < 0.01$ (increase = red; decrease = blue) and $p < 0.001$ (increase = yellow; decrease = light blue). The right hemisphere (Dx) is on the reader’s left according to neuroradiological standard. The numbers refer to Brodmann’s nomenclature. The derived PET images have been superimposed on a Computerized Brain Atlas transformed normal MRI image. Thal, thalamus; V, vermis.

according to the painful side. A correlation analysis of the cerebral activity between the BA9/32, the BA24, and the anterior thalamus of both sides revealed a strong negative correlation only between the right BA9/32 and the right anterior thalamus regardless of the painful side (Fig. 3). The regions of interest drawn for post-hoc analysis (Figs 2 and 3) were made according to the contours of the engaged regions in Figure 1 (omnibus significance maps) and the database of the Computerized Brain Atlas (Greitz et al., 1991). Also, an activation was present in the right part of the cerebellar vermis.

The prefrontal cortex demonstrated decreased activity during pain in the regions of BA10, 45, and 46 (Table 2). No activity change was detected in the upper brain stem. The basal forebrain (orbitofrontal cortex, infralimbic region), and the lower brain stem were incompletely sampled in some patients due to motion, and were therefore excluded from analysis.

DISCUSSION

We do not consider that the placebo effect severely confounded the results, although patients’ preconceived expectation of analgesia could not be excluded. However, the magnitude of relief achieved with PCGS was beyond the extend that could be explained by placebo alone. Notwithstanding, some of the patients in the present study had previously received single-blinded dummy stimulation without proven analgesic efficacy (Meyerson et al., 1993). Since it is not our intention to address the therapeutic mechanism of PCGS in this communication, ethical concerns precluded the possibility of conducting double-blinded PET experiments on patients with debilitating and protracted suffering, since it would cause unnecessary pain by denying them one treatment cycle.

Surprisingly, we did not find any detectable rCBF change underlying the stimulating electrodes.
FIG. 2. rCBF in the BA24, the BA9/23 and the anterior limbic thalamus illustrating the preferential right-involvement regardless of the side of the PTN pain. The rCBF values correspond to the averaged readout of the contiguous regions-of-interest, drawn according to the p-map of each region. The values of the left BA24 were obtained in a manner similar to that for the right BA24. The data are displayed as mean ± SEM. The activity in the right BA24 during habitual painful state was significantly higher than that in the left (paired t-test, p < 0.001). Note that PCGS resulted in a tendency toward normalization of the activity pattern in the two hemispheres. The rCBF changes in BA24 reflects the treatment efficacy evidenced by the dramatic decrease of pain ratings using VAS.
CENTRAL PROCESSING OF TRIGEMINAL NEUROPATHIC PAIN

FIG. 3. Correlation analysis between the right anterior limbic thalamus and the right dorsal MPFC (BA9/32). Strong negative correlation between the rCBF in BA9/32 and the anterior limbic thalamus was present regardless of the side of the painful trigeminal neuropathy [left (■) \( r = 0.883 \); right (○) \( r = 0.908 \)]. Data presented were the individual averages of repeated measurement of different conditions (5 patients; 3 conditions; 15 averaged data points).

during PCGS or pain-alleviated states. The absence of rCBF change was corroborated by a previous PET study on two patients suffering from post-stroke pain, refractory to other treatments except for PCGS (Peyron et al., 1995). In our patients, the orientation and placement of the electrode array was individually specific in order to obtain analgesic efficacy. The inhomogeneity of electrode positioning, taking into account the side difference, might obscure the rCBF change using current image treatment. Another possibility is that an induced inhibitory activity underlying or adjacent to the stimulating electrode resulted in a net absence of rCBF change (Sharp et al., 1988).

To elucidate an asymmetric brain mechanism for the processing of chronic pain, one should avoid employing pain-inducing procedures, since the central representation may be confounded with a motor intent of escape (Hsieh et al., 1994). The linked activation of the primary somatosensory/motor area (contralateral), the mid-posterior insula/putamen (connecting to primary somatosensory area, more contralaterally expressed), the ACC (BA24, contralateral), the supplementary motor and premotor areas (more contralaterally expressed), the cerebellum (part of the motor engram), and the contralateral posterior thalamus (relaying nociceptive input), demonstrated in studies of experimentally induced acute unilateral phasic pain (Jones et al., 1991; Talbot et al., 1991; Casey et al., 1994; Coghill et al., 1994; Derbyshire et al., 1994; Davis et al., 1997; Svensson et al., 1997), reflects the behaviourally motivational effect (Hsieh et al., 1996b). This pattern of central processing represents the intention to initiate or inhibit an escaping motor behaviour contingent upon the perception of acute lateralized pain. The activation in the contralateral caudal BA24 during experimentally-induced acute pain, functionally codes the laterality of the somatosensory input, and facilitates the targeting of areas subserving plans for movement (supplemental motor area, premotor area, and cingulate motor area) and to initiate other behavioural responses (Hsieh et al., 1994, 1996b). Recent pain imaging studies on tonic heat (Derbyshire & Jones, 1998) and chemogenic pain (Iadarola et al., 1998) have revealed a more bilaterally expressed activation in the ACC. It is tempting to suggest that the diversity in central processing of pain is more context-dependent (pertaining to the experience and the associated cognitive evaluation of pain) rather than to the type of noxious stimulation employed (Hsieh, 1995; Ingvar & Hsieh, 1999).

Brain imaging studies of clinical pain syndromes (Hsieh et al., 1995a, 1996b), which do not initiate escape behaviour, have consistently revealed a right-hemispheric preference in the appreciation and the appraisal of pain (the ACC and the MPFC; BA24, 32/9). In this study, we have provided further evidence for such a right-sided preponderance (Fig. 1). Neuropathic pain reflects a change in the normal functions of the peripheral or central nervous system, and the sustained pain is present in the absence of acute noxious stimuli and nocifensive reflex behaviour. This pattern of a more right-sided expression was corroborated by a recent PET study on experimental cranial pain elicited by capsaicin (May et al., 1998). These congruent findings support our theory that pain devoid of the aforementioned motivational component of escape behaviour preferentially targets the right hemisphere.
particularly the BA24 (Hsieh et al., 1996b). The differences between the activation patterns of acute intense pain and chronic sustained pain conform to the current neuropsychological theories of hemispheric asymmetries in the limbic regulation of affect and cognition (Liotti & Tucker, 1995). The commonly observed involvement of the right ACC (BA 24 and also 9/32) in pain-imaging studies of sustained pathological pain, supports its crucial role in pain suffering. Hypnotic suggestion has been demonstrated to effectively modulate the expression of the ACC on affective encoding of pain (Rainville et al., 1997). The right hemisphere in humans has been proposed to be preferentially involved in functions of emotional arousal and associative learning from aversive stimuli, e.g. pain, intimately linked to the generation of autonomic components of the emotional response (Gainotti et al., 1993; Hugdahl, 1995). It is noteworthy that while the right BA24 demonstrated heightened activity during pain, the activity in the left BA24 was significantly lower (Fig. 2) as previously demonstrated during provoked cluster headache attacks (Hsieh et al., 1996b). Pain relief obtained with PCGS showed a concomitant trend to restore the cerebral activity in both sides (Fig. 2). Thus, the activity change in the right BA24 presumably reflects as a measure of treatment efficacy. Both painful trigeminal neuropathy and cluster headache involve the trigeminal system and correspondingly activated the same region in the right ACC, which can be distinguished from that of painful mononeuropathy in the lower extremities (Hsieh et al., 1995a, 1996b). In the case of painful mononeuropathy, pain of either leg spatially activated the same region in the right BA24. These observations suggest a possible spatial organization for pain-directed attention in the right caudal BA24, similar to a somatotopically-organized cognition-directed attention in the caudal-most BA32/24 (Paus et al., 1993) and cingulate motor (Morecraft & Hoesen, 1992; Dum & Strick, 1993; Schlaug et al., 1994).

The significance of deactivations in general, and during pain, has previously been discussed in detail (Hsieh et al., 1995a, 1995b, 1996a, 1996b, 1999; Ingvar & Hsieh, 1999). Since the rCBF changes are tightly coupled to the levels of regional neuronal activity (Raichle, 1987), the increase and decrease of rCBF accordingly indicate either an increased or a diminished net neuronal activity, respectively, and therefore physiologically imply a paradigm-specific (compared to the reference state), functional activation or inhibition/disengagement of the involved brain regions (Haxby et al., 1994; Hsieh, 1995; Ghatan et al., 1998). We have demonstrated consistent and neurophysiologically/neuropsychologically meaningful patterns of reduced cerebral activity in the prefrontal cortex in studies of acute nociceptive pain (Hsieh et al., 1996a), provoked episodic cluster headache attacks (Hsieh et al., 1996b), and endurable sustained experimental pain (Hsieh et al., 1999). Therefore, we also examined the deactivation pattern of cerebral activity in the prefrontal region in the presence of a chronic sustained pain.

All patients in this study had a history of episodes of depression and suicidal ideation due to the intractability of the disease prior to the implementation of PCGS. The frequent co-occurrence of chronic pain, depression and impaired cognitive performance (Eccleston, 1994, 1995; Diener et al., 1995) has long attracted the attention of pain researchers, and is unequivocally an important clinical phenomenon. There is evidence that the right hemisphere is specialized to become activated by and to process negative emotional reactions (Davidson et al., 1990; Davidson, 1995). Consequently, the right hemisphere has been proposed to be crucial in co-occurrence of pain and depression (Otto et al., 1989; Schiff & Lamon, 1994). This hypothesis is corroborated by studies examining the psychopathology in response to focal brain injury (Gainotti, 1972; Robinson & Downhill, 1995), the behavioural and emotional effects of pharmacological inactivation of one hemisphere (Terzian, 1964; Lee et al., 1988), the differential activation of the hemispheres during different states of mood (Tucker, 1981), the neuropsychological performance of depressed patients (Kronfol et al., 1978), and behavioural indices of hemispheric arousal in negative emotional states (Hatta, 1985). The biochemical and pharmacological correlates to pain and depression may
relate to a dysfunction of, for example, the serotonergic system (Eberhard et al., 1989; Yaksh & Malmberg, 1994).

The right BA9/32 of MPFC/ACC has been demonstrated to be consistently involved in pain-related events. It is either activated by a provoked cluster headache (Hsieh et al., 1996b) and by anticipating a novel/impending painful stimulus (Hsieh et al., 1999), or deactivated as illustrated in the present study. In normal subjects, this region of the right MPFC (BA9) displays a higher serotonergic activity than the left (Arato et al., 1991). MPFC (BA9) and ACC (BA32) are regions essential for executive cognitive functions (Buckner et al., 1995; Fletcher et al., 1995; Ghatan et al., 1995, 1998; MacLeod et al., 1995), and possibly crucial for normal behaviour (Arato et al., 1991; Liddle et al., 1992). On the day of the PET examination, suffering from the excruciating pain due to the overnight abstention from PCGS was expressed by patients. It is conceivable that the reappearance of pain (habitual-pain state) elicited negative effects. The rCBF pattern in this study partially conforms to that observed in patients with depression and cognitive impairment (Bench et al., 1992; Dolan et al., 1992). Recent PET studies in patients with depression has demonstrated a decreased activity in the left MPFC/ACC (lower BA 9/32) and the left dorso-lateral prefrontal cortex [approximately BA 45/46; (Bench et al., 1992; Dolan et al., 1992, 1993)]. In patients with marked cognitive impairment associated with depression, there was a further decreased activity in the left frontopolar region (BA 10), combined with a concomitant increased activity in the right cerebellar vermis [(Bench et al., 1992; Dolan et al., 1992, 1993); cf. Fig. 1 and (Hsieh et al., 1995a)]. The deactivation/activation pattern of the aforementioned regions in the present study suggests that our patients were cognitively impaired when examined during their incapacitating habitual pain of high intensity. The differential pattern of activity in the subregions of the ACC, with decreased activity in the cognition-related BA9/32, combined with increased activity in the pain-related BA 24, conceivably corresponds to the interference of attention to pain upon the attention capacity for cognition (Kahneman, 1973; McCaul & Malott, 1984; Devinsky et al., 1993; Eccleston, 1994, 1995; Eccleston et al., 1997). Deactivation in other regions (right BA 10/46, bilateral BA46/45) known to be involved in cognitive planning and sustained attention (Goldman-Rakic, 1987; Fuster, 1989), can also be interpreted in the context of the intrusive nature of sustained high-intensity pain and its disruptive effect on the normal function of the mind (Price, 1988).

To our knowledge, this is the first pain-imaging study that demonstrates a heightened activity in the anterior limbic thalamus during spontaneous, sustained pain of high intensity. Brain imaging studies on experimental pain (see references above) have demonstrated an activation mainly in the posterior thalamus, relaying the noceptive information, while our previous PET study of peripheral mononeuropathic pain showed a deactivation of the posterior thalamus (Hsieh et al., 1995a). The lack of a contralateral deactivation in the posterior thalamus in the present study is probably due to the method used to map the common regions of involvement by pooling the images from lateralized PTN together. The activation in the anterior thalamus, with a local maximum located at the mediodorsal nucleus, spatially encompassed the whole limbic thalamus (Bentivoglio et al., 1993), but spared the relaying posterior thalamic nuclei. The mediodorsal nucleus, which is heavily interconnected with prefrontal cortex, projects to cingulate fields. The limbic thalamus subserves the affective processing of pain and plays a critical role in the formation and storage of mnemonic traces related to behavioural learning of pain in non-human primates and humans (Bentivoglio et al., 1993; Devinsky & Luciano, 1993). The strong negative correlation (Fig. 3) between the activity in the right MPFC/ACC (BA 9/32), which was decreased, and the activity in the right anterior thalamus, which was increased during pain, indicates a plasticity and functional reciprocity developed as a result of the sustained chronic pain of extreme intensity (Friston et al., 1995). We did not observe such a correlation pattern in our PET studies of episodic cluster headache, anticipation of pain, experimentally-induced acute
pain and chronic neuropathic pain of mild-to-moderate degree (Hsieh, 1995; Hsieh et al., 1995a, 1995b; 1996a, 1996b, 1999; Ingvar & Hsieh 1999). It is tempting to speculate that sustained incapacitating PTN pain/suffering activates the BA24 and kindles the limbic–thalamus–cortical circuit for pain effect and psychological responses (Bentivoglio et al., 1993; Craig, 1995). As a consequence, this constant emotional stress may lead to an inhibition of neural substrates subserving the cognitive performance (Figs 1 and 3). Our data are corroborated by a previous PET study on signal transduction and neural association between discrete cerebral regions (Kusuki et al., 1995). The authors used C-11-labelled diacylglycerol to probe the activity of phosphatidylinositol turnover rate as an indicator of neuronal activity. In their study, PCGS in patients with central pain syndrome normalized the hyperactivity in the thalamus and potentiated the suppressed prefrontal cortex activity (Kusuki et al., 1995). In our study, pain alleviation with the therapeutic PCGS reinstated the activity in these prefrontal regions (Figs 1-3) and attenuated the hyperactivity in the medial thalamus and the anterior cingulate cortex. It is tempting to suggest that the activity change effected by the PCGS presumably reflect the positive effect on the mood and cognition in our patients.

Conclusion

This study corroborates the involvement of the ACC as being a critical part of the processing of chronic pain, and also points to the involvement of the anterior thalamus in conjunction with the frontal cortex. The data support a preferential role for the right hemisphere in pain-processing, as illustrated by the right preponderant changes in this group of patients with mixed left and right-sided pain affliction. Our study not only verifies the preferential role of the non-dominant hemisphere in the appreciation of pain suffering, but further supports that sustained chronic pain, being devoid of the motivational component of an escape response, targets the non-dominant hemisphere.

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