

Right-lateralised central processing for pain of nitroglycerin-induced cluster headache

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Summary Recent functional brain imaging studies with positron emission tomography (PET) suggest a preference of the right hemisphere, especially the anterior cingulate cortex (ACC), in affective processing of the clinical pain syndromes. We have investigated the central processing of cluster headache (CH) attacks provoked by sublingual nitroglycerin (NTG). In the cerebrum, provoked CH activated the ACC and the temporopolar region of the right hemisphere in addition to other regions. The regions activated in the ACC (Brodmann area (BA) 24 and 32) are involved in affective/cognitive processing of pain and willed attention. Our study discloses the preferential role of the right hemisphere in attributing emotional valence and attention to the suffering of pain. The findings support the theory of a right hemispheric specialisation in the mediation of withdrawal-related negative affect. The divergence of the distributed central processing between provoked cluster headache attack and experimentally induced acute pain indicates different central mechanisms for different types of pain.

Key words: Positron emission tomography; Regional cerebral blood flow; Cluster headache; Brain activation; Anterior cingulate cortex; Brain asymmetry

Introduction

Previous regional cerebral blood flow (rCBF) studies have emphasised a dysfunction of the cerebrovascular regulation in headache while little study has been conducted to evaluate the central pain processing of headache (Russell and Fanciullacci 1993). Considering the pervasive impact of episodic cluster headache (CH) on patients, elucidation of the brain events during headache attacks would be contributing to the

understanding of the central mechanisms of CH and could provide information that would demonstrate the relevance of studies on experimentally induced pain in man. Despite the previous efforts using ¹³³Xe-single photon emission computed tomography (SPECT) to study the regional cerebral blood flow (rCBF) response in the CH, no conclusive findings have yet been reported (Russell and Fanciullacci 1993).

Neuropsychological studies involving electrophysiological measures and clinical observations on patients with unilateral frontal lesions have suggested the specialisation of the anterior right hemisphere (e.g. prefrontal and anterior temporal regions (Davidson 1995)) in the mediation of withdrawal-related negative affect, e.g. fear and disgust. On the other hand, the corresponding areas of left hemisphere seems to be more connected to approach-related emotions, e.g. happiness and amusement (Davidson et al. 1990). It has also been suggested that the right hemisphere in humans is preferentially involved in functions of emotional arousal and associative learning from aversive stimuli (e.g. pain), intimately linked to the generation of the autonomic components of the emotional response, while the left

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* Corresponding author: Abbreviations: ACC: anterior cingulate cortex; BA: Brodmann area; CBA: computerised brain atlas; CH: cluster headache; CS: cavernous sinus; Dx: right; NS: nasal/paranasal sinus; NTG: nitroglycerin; PET: positron emission tomography; PFC: prefrontal cortex; PM: premotor area; rCBF: regional cerebral blood flow; Si: left; SMA: supplementary motor area; VAS: visual analogue scale.

hemisphere seems to play a more important role in functions of intentional control of the emotional expressive apparatus (Gainotti et al. 1993; Wittling 1995).

The anterior cingulate cortex (ACC, Brodmann (BA) 24) is an area involved in the emotion-regulated attention to pain (for a review see Bouckoms (1994) and Devinsky et al. (1995)). In patients with ongoing peripheral neuropathic pain, we have previously reported that only the right side of this region is activated regardless if the pain emanated from the right or the left leg (Hsieh et al. 1995a). In this study, we set out to investigate the validity of the preferential activation of the right ACC as a general phenomenon for other clinical pain syndromes.

A CH attack can be elicited with sublingual nitroglycerin with high certainty during a patient's active cluster period and without significant side effects (Ekbohm 1968). The attack and the provoked pain can be rapidly and effectively aborted with serotonin (5-HT₁)-like agonist sumatriptan (Sumatriptan cluster headache study group 1991). We used positron emission tomography (PET), measuring rCBF as an index of regional neuronal activity, to investigate the central processing of provoked CH attacks with special references to the right prefrontal cortex, the ACC, and the right temporal cortex.

Materials and methods

The study was approved by the local Ethics and Radiation Safety committees at the Karolinska Hospital. Informed consent was given by all the subjects. We studied seven right-handed patients (mean age 45 years (SD = 6); five male and two female) with episodic CH according to the International Headache Society classification (IHS 1988). The patients had not had any CH attack for the last 8 h and had not taken any drug at least 15 h before the study. They were free of any other organic (space-occupying) brain disease and psychiatric disorder.

CH attack was provoked by sublingual administration of nitroglycerin (NTG, 1 mg). Patients rated their headache intensity with a 100-mm visual analogue scales (VAS; anchored with '0 = not at all' and '100 = the worst imaginable'). We used [¹⁵O]butanol as the tracer for rCBF. Each patient was subjected to six consecutive rCBF (uptake) studies: A — baseline one (rest); B — baseline two (rest, 10 min after A); C — NTG, 5 min after sublingual NTG (1 mg) administration; D — headache one (when VAS ≈ 70 mm); E — headache two (10 min after D); F — pain relief (when VAS ≈ 10 mm) obtained with subcutaneous injection of sumatriptan (6 mg). Subjective description and physical signs validating the attack of CH (e.g. lateralised pain, conjunctiva injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and eyelid edema) were monitored.

The image analysis and statistical treatment have been described (Hsieh et al. 1996; Ingvar et al. 1994). The PET scanning (ECAT EXACT HR, Siemens, Germany (Wienhard et al. 1994)) of brain tissue radioactivity (100 sec uptake image, uptake reflecting rCBF (Ingvar et al. 1994)) was commenced simultaneously with the injection of [¹⁵O]butanol (the rCBF tracer, half life = 123 sec, 25 mCi, 62 MBq). Subjects' eyes remained closed during actual scanning and the light was dimmed. To correct for head movements between scans, all the scans were aligned with respect to the first one of each individual, using the Automated Image Registration software (Woods et al. 1993). Images were stereotactically reformatted (2.6 × 2.6 × 2.8 mm, 48 slices, with Computerized Brain Atlas (CBA) procedure (Greitz et al. 1991)), normalised and filtered with 16 mm FWHM to generate state-

dependent omnibus significance maps (*P*-maps). Based on the observations of the transcranial Doppler studies that the NTG does not significantly increase CBF of common carotid artery in CH patients in the cluster period (Hannerz and Jogestrand 1992), the ¹³³Xe-SPECT studies that there is no change of mean global CBF during CH attack in comparison with resting control (Dahl et al. 1990; Krabbe et al. 1984), and the ^{99m}Tc-hexamethyl-propyleneamineoxime-SPECT study that the therapeutic dose of sumatriptan (6 mg) does not alter the cerebral perfusion (Ferrari et al. 1995), we normalise the rCBF to a global mean of 50 nCi/ml in order to remove possible confounding attribution from pharmacological intervention and ventilatory influence on the global CBF (Fox and Mintum 1989; Ingvar et al. 1994). To address the central processing of pain, CH attack (headaches 1 and 2) was compared to the resting control (baselines 1 and 2). 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-max) with multiple comparison adjustment (Friston et al. 1991; Ingvar et al. 1994). Regions-of-interest (ROI, anatomical structures and Brodmann areas (BA) (Brodmann 1909)) were designated according to the brain database implemented in the CBA (Greitz et al. 1991).

Since we observed prominently increased radioactivity in the cavernous sinus (CS) during provoked CH attack from the above analytic procedure (see Results), a temporal analysis of radioactivity in the CS was conducted. ROI was defined from a superimposed CBA-processed MRI image of a normal subject. Similar statistical treatment for image analysis was performed. For the hemodynamics profile in the CS, scans C–F were respectively compared to B. Scan B contained the NTG effect on the hemodynamics in the CS. Scan F reflected the effect of subcutaneous injection of sumatriptan (6 mg) on the hemodynamics in the CS.

Results

Four of the patients (three males, one female) remained in active cluster period while three of the patients were out of their cluster period by the time the experiment was conducted. Typical lateralised CH attack (right CH = 2, left CH = 2), subjectively and objectively confirmed (excruciating lateralised headache with maximal VAS ≤ 90–100 mm, lacrimation, profuse sweating in the forehead, rhinorrhea, miosis, ptosis, and eyelid edema), was successfully provoked within 18–35 min after the administration of NTG in four patients during their cluster periods and promptly relieved (within 5–10 min) with subcutaneous administration of sumatriptan. These four patients were designated as NTG-positive patients. Patients subjectively described the quality of pain as 'horrendous, intolerable and dreadful suffering'. During the provoked CH attack, hyperventilation, sustained facial grimacing, teeth clenching, and immensely tonic contraction of bilateral upper and lower extremities were conspicuously observed in all of the NTG-positive patients. CH attack was not provoked in the other three patients (designated as NTG-negative) out of their cluster period. They were followed until 90 min after the administration of NTG.

During the CH attack, the rCBF significantly increased in the right caudal ACC (BA24) and the rostrocaudal ACC (medial prefrontal cortex BA 32/9; local maximum located in between and activation spatially encompassed both regions), temporopolar region (BA38), sup-

plementary motor area (SMA, medial BA6, activation spatially encompasses both sides), bilaterally in the primary motor area (foci corresponding to face, upper and lower extremities, respectively), premotor areas (PM, lateral BA6), opercular region (BA44,45), insula (BA14)/putamen, and lateral inferior frontal cortex (BA47) (Table I; Fig. 1). We observed reduction in rCBF in the bilateral posterior parietal cortex (BA7,40), occipito-temporal region (BA37,19) and prefrontal cortex (BA10) (Table I; Fig. 1). Since the field-of-view of the employed ECAT EXACT HR encompassed the whole head, we also observed prominently increased activity in the bilateral CS and the nasal/paranasal sinus (NS) (Fig. 1).

In the temporal analysis of the radioactivity in the CS, NTG prominently increased the radioactivity in the CS for both NTG-positive and NTG-negative patients (Fig. 2). Radioactivity in the CS further increased and remained when the pain intensity of CH attack peaked (headache-1, VAS \geq 70–100 mm; headache-2, VAS \geq 90–100 mm). The radioactivity in the CS was low following the relief of CH, obtained within 10 min of the administration of sumatriptan. We measured the CS-radioactivity in one NTG-negative patient, sampled in a similar time course as the NTG-positive group. The

increased radioactivity declined after the NTG-administration and reached the control level at the end of the experiment.

Discussion

The procedure of provoking CH with NTG has been used in the clinical setting and been proven to be safe (Ekbohm 1968). Still it is of ethical concern whether it is permissible to provoke a pain of the magnitude that is close to the tolerance limit in patients. Based on this line of reasoning we decided to keep the study group at the absolute minimum that the sensitivity of the employed methods allow. The regions identified in this study represent cerebral areas most consistently involved in the central processing of pain during a provoked CH attack on a group level. Lateralised NTG-positive patients were grouped together for the analysis of general central representation due to the limited sample size. Regions of contralateralised (e.g. thalamus) and/or possible distinct involvement may be obscured while the common areas of activation/deactivation are preserved (Fig. 3; Hsieh et al. 1995a).

CH attack activated the caudal BA24 of the ACC. As evidenced by the clinical observations that limbic

TABLE I
FOCI OF SIGNIFICANT CHANGE OF rGBF: CLUSTER HEADACHE VS. BASELINE

Region	Brodmann area	Right					Left				
		x	y	z	Z-max	$\Delta\%$ -rCBF	x	y	z	Z-max	$\Delta\%$ -rCBF
Precentral	M1 (leg)	23	-29	57	2.8**	7.4	-28	-32	58	2.6**	7.4
Precentral	M1 (arm)	51	-17	37	4.6***	9.2	-49	-15	37	4.1***	9.8
Precentral	M1 (face)	57	-3	16	4.3***	8.4	-49	-6	21	3.8**	5.5
Precentral	6 (PM)	44	8	46	3.6**	7.8	-39	6	48	3.6**	8.4
Precentral	6/8 (SMA)	3	20	53	2.8**	9.8					
Sup post parietal	7	18	-55	56	4.1***	-7.8	-8	-57	55	3.2**	-7.4
Sup frontal	10	13	62	-2	3.1**	-4.1	-25	51	-10	3.3**	-5.1
Occipital	19						-36	-64	23	3.6**	-6.6
Ant cingulate	24	8	-15	40	3.1**	7.0					
Ant cingulate	31	15	-55	25	2.82**	-7.8					
Ant cingulate	32/9	5	34	34	3.9***	7.4					
Inf temporal	37	48	-52	-8	3.5**	-6.6	-51	-48	-7	4.5***	-12.1
Temporopolar	38	49	10	-10	3.8***	5.9					
Inf post parietal	40						-52	-36	40	3.4**	-5.2
Pars opercularis	44	50	11	9	3.8***	7.4					
Pars triangularis	45	49	22	8	3.7**	6.9	-52	20	9		6.0
Lat inf frontal	47	42	25	-8	3.5**	6.6	-40	18	-7	3.6**	8.8
Insula/putamen	14	24	-6	11	3.6**	7.0	-32	18	11	3.9***	8.4

Stereotaxic coordinates of peak activation (Talairach and Tournoux 1988) are expressed in millimetres 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). Ant: anterior; post: posterior; sup: superior; inf: inferior; lat: lateral; MI: primary motor area; SMA: supplementary motor area; PM: premotor area.

** $P < 0.01$.

*** $P < 0.001$.

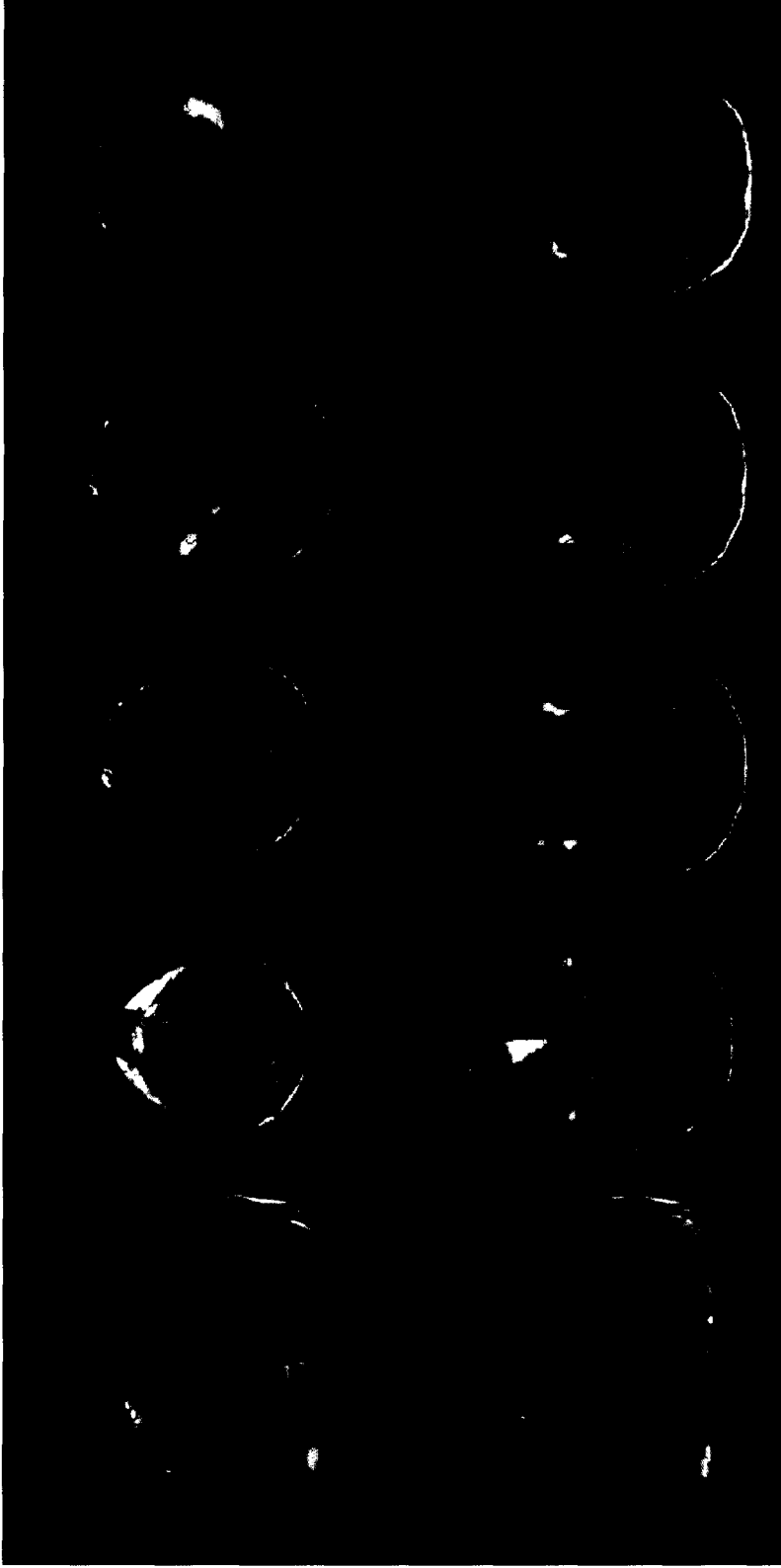


Fig. 1. Cerebral areas of significant changes in rCBF during attack of cluster headache. The omnibus significance maps (P -maps) are color-coded into four levels defined by $0.001 \leq P < 0.01$ (increase = red; decrease = blue) and $P < 0.001$ (increase = yellow; decrease = light blue). The right hemisphere (Dx) is on the reader's left according to the neuroradiological standard. The numbers refer to Brodmann's nomenclature (Ins: insula; MI: primary motor area; SMA: supplementary motor area). Cavernous sinus (CS) and nasal sinus (NS) show markedly increased activity (Z -max = 3.8, $P < 0.001$ and Z -max = 3.9, $P < 0.001$, respectively). For anatomic illustration, the derived PET images were in the figures superimposed on a CBA-transformed, normal MRI image.

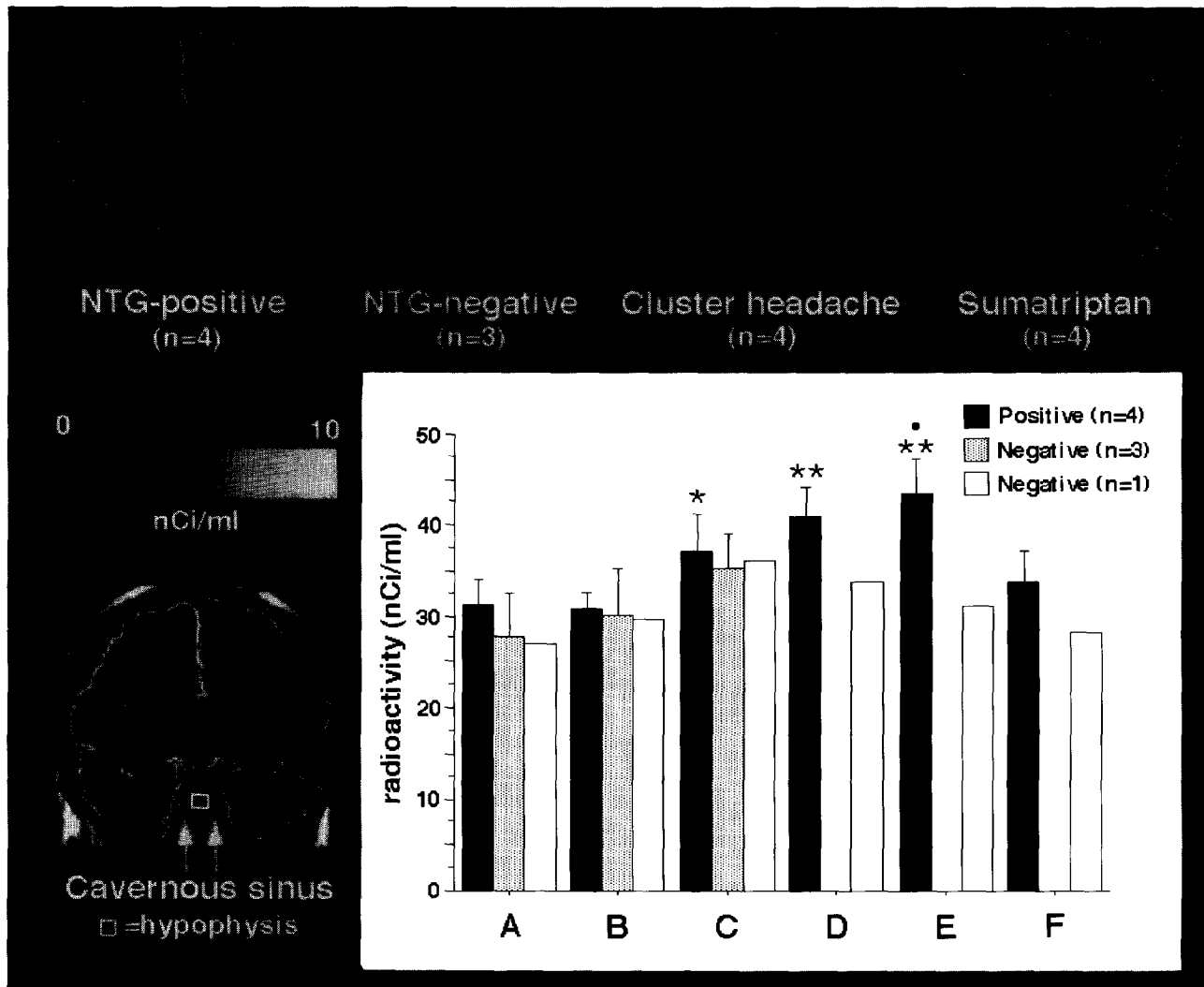


Fig. 2. Temporal profile of radioactivity in the cavernous sinus (CS). Images depict the averaged difference (pixel-by-pixel) of normalized radioactivity in the CS (region defined on the CBA-processed MRI) between different states vs. the baseline 2 of NTG-positive and -negative group, respectively. The 'Cluster headache' image is a composite image of headaches 1 and 2 vs. baselines 1 and 2. The bar chart denotes the state/time course of radioactivity (mean \pm SEM) in the CS (compared to baseline 2; * $P < 0.05$; ** $P < 0.01$). The comparison between headache 2 vs. NTG achieved significant level of $P < 0.05$ (●). One case of the NTG-negative group was sampled in a similar time course as the NTG-positive group and revealed a decline of radioactivity. For labels A-F, see the method. The local maxima of different comparisons did not located at the same section displayed in the figure.

forebrain surgery (e.g. cingulotomy) alleviates the affective impact, attention and cognitive appraisal of intractable pain while preserving the perception of pain, the ACC attributes emotional valence and attention to the suffering of pain (for a review see Bouckoms (1994)) and possibly modulate the affective signals from the limbic system (Davis et al. 1994; Hsieh et al. 1995c). The caudal BA24 has consistently been demonstrated with PET to be activated in studies on experimental and clinical pain (for a review, see Hsieh et al. (1995a)) and unpleasant itch (Hsieh et al. 1994; Hsieh et al. 1995b). This region anatomically corresponds to the BA24' (Vogt et al. 1995) and has been proposed to be par-

ticularly pertinent to central pain processing and mediate versatile executive functions: generating an affective component, organising motor responses, memory associated with predicting and avoiding such stimuli, response selection and attention to aversive input (Devinsky et al. 1995; Vogt et al. 1993). In addition, CH attack activated rostrocaudal ACC (BA32/9), a major component of the anterior attentional system subserving versatile willed attention (Frith et al. 1991; Pardo et al. 1990; Paus et al. 1993). The activation in the temporopolar region (BA38) may mirror the excruciating quality of the provoked CH. Patients described the experienced pain as 'horrendous, intolerable and dread-

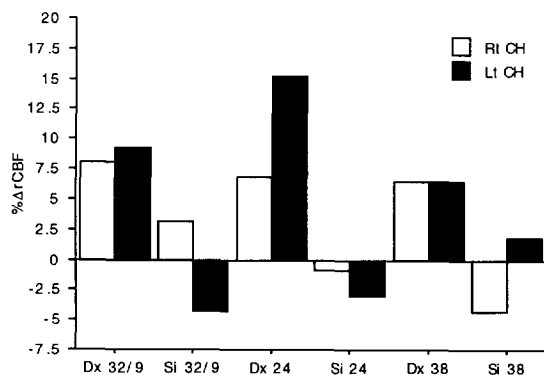


Fig. 3. Right preferential activation regardless of the side of painful input. The NTG-positive patients were grouped according to their painful side (Rt = 2, Lt = 2). ROIs (drawn from the composite activation maps, Fig. 1) displayed are the preferentially activated regions in the right hemisphere (Dx). The mean magnitude of change in rCBF ($\Delta\%$, averaged across activated contiguous slices) between CH attack and resting control were depicted. Activity in the homologous regions in the left hemisphere (Si) were measured in the same manner. The consistence and coherence of increased activity in the right hemisphere (Dx 32/9, Dx 24, and Dx 38) during pain regardless of the painful side was demonstrated. Regions of prominent concordant change of activity were preserved, whereas those with discordant or small magnitude of responses (inhibition of Si 24) were obscured in the significance maps (Fig. 1).

ful suffering'. Temporopolar stimulation in human can elicit fear (Penfield and Jasper 1954) while in non-human primates produce a syndrome characterised by behavioural inhibition, apparent hypervigilance, and altered facial expressions seemingly reflecting 'arousal, attention or anxiety' (Kaada 1960).

The distinct findings that the right ACC/medial prefrontal cortex (BA24, 32/9; Fig. 1Dx,d) and the right temporopolar region (BA38) were preferentially activated in our four right-handed patients during CH attack are consistent with our recent PET studies on the right-handed patients with chronic ongoing neuropathic pain (painful mononeuropathy (Hsieh et al. 1995a)) and painful trigeminal neuropathy regardless of the side of infliction (Hsieh et al., unpublished). The caudal portion of the right BA24 has also been demonstrated with PET in the right-handed normal subjects to participate in the attentional modulation (cognitive appraisal) on pain-relevant anticipation imposed with different psychological disposition (Hsieh 1995; Hsieh et al. 1995c; Hsieh et al. 1996). In a recent PET study on spontaneous migraine of right-sided headache, the maximal activation (Z-score maximum) of the ACC (BA24/32) was located in the right ACC (Weiller et al. 1995). We reported a similar activation pattern of the BA24/32 in a PET study on traumatic nociceptive pain inflicted in the right upper arm of right-handed normal subjects (Hsieh et al. 1996).

Experimental and clinical studies have demonstrated that pain sensitivity is lateralised in humans, with the non-dominant hemisphere manifesting a relatively higher response than the dominant hemisphere (Schiff and Gagliese 1994; Wittling 1995). Studies on examining pain threshold or pain tolerance by means of various experimental pain-inducing procedures revealed a lower pain threshold or pain tolerance when noxious stimuli are applied to the left side of the body in right-handers. Pain sensitivity is reversed in most cases in the left-handers (Göbel and Westphal 1987). With respect to clinical studies, pain endurance was found 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). Right brain damage affected pain sensitivity both in the contralateral paralysed arm and in the ipsilateral healthy arm, whereas left brain damage affected only the contralateral paralysed arm (Neri et al. 1985). Studies on patients with psychogenic pain, rheumatic pain, and hysterical conversion reactions have also demonstrated a more consistent lateralisation (although debated) of pain to the left side of the body (Merskey and Watson 1979). Increased psychological disturbance (depression, hypochondriasis and hysteria rated by The Minnesota Multiphasic Personality Inventory) was observed in the left-sided chronic pain patients (Schiff and Gagliese 1994). A suggested lateralisation of brain neurotransmitters seems to end in a correspondence with lateralisation in neurophysiological and psychological functions (Wittling 1995). Norepinephrine and serotonin, involved in the upregulation or downregulation of autonomic and psychological arousal, show a relatively higher concentration/activity in the right side of the human and animal brain (Arato et al. 1991; Barnéoud et al. 1990; Mayberg et al. 1988; Oke et al. 1978). In contrast, neurotransmitters being more intimately involved in the control of motor behaviour and higher integrative functions (e.g. dopamine) favour the left side of the human brain (Glick et al. 1982; Wagner et al. 1983). These neurochemical studies lend support to the theories that the right (non-dominant) hemisphere is more involved in emotional arousal in the withdrawal-related negative affect, e.g. aversive pain (Davidson 1995; Gainotti et al. 1993; Hsieh 1995; Wittling 1995). It is remarkable that a right hemispheric asymmetry of higher serotonergic activity in normal humans has been elegantly demonstrated in the activated right medial prefrontal cortex (BA 32/9) than the left corresponding region (Arato et al. 1991). The observations are further corroborated by a recent report on brain electrical source analysis of laser evoked potentials in response to painful trigeminal nerve stimulation (Broom and Chen 1995). While applying the painful stimulus on the right temple and forehead, dipole III (in the medial prefrontal cortex approximating the BA32/9, ascribed with mechanism of

attention and arousal by the authors) was identified to locate in the right hemisphere.

The propensity of activation in the ACC in various pain imaging studies highlights its role as one key to the suffering of pain (Hsieh et al. 1995a; Hsieh 1995). The observations on functional specialisation of the ACC in attributing emotion suggest that pain of different affective-cognitive contents may involve the ACC (BA24) of different hemispheres and engage different neural circuits that subserve tangled psychological and behavioural functions. Recognition of faces that expressed emotional content activated the right mid-cingulate ACC (BA 24) (George et al. 1993). Complex emotions, e.g. sadness, activate the rostral ACC (BA 24) in both hemispheres (George et al. 1995). Since the Emotional Stroop Task (a neuropsychological test that implicitly attracts the subject's attention to affect-laden words) mandates actively the suppression of inappropriate verbal response (left-hemispheric specialisation), it activated mainly the left caudal BA24 and/or 32 in normal subjects (George et al. 1994). The demonstrated inverse correlation between the left BA24 and the left language areas pinpoints a functional linkage and reciprocity during the task (George et al. 1994). An acute noxious stimulus elicits immediate nocifensive reflex of withdrawal. It is the very nature of acute intense pain that is registered and analysed in terms of impending motor response contingent upon the attention to the perceived aversive input (Hsieh et al. 1995b). The contralateralised activation of the BA24, found in studies on experimentally induced acute pain and itch (Casey et al. 1994; Coghill et al. 1994; Hsieh et al. 1994; Jones et al. 1991; Talbot et al. 1991), functionally codes the laterality of the challenging somatosensory input with affection-regulated attention and instigates a behaviourally motivating affect (e.g., intention/urgency contingent upon the unpleasantness) (Hsieh et al. 1994; Hsieh et al. 1995b; Talbot et al. 1991). The interpretation is substantiated by the evidence that acute itch activated the ipsilateral SMA and the contralateral BA24 while acute pain activated contralaterally both the SMA and BA24 (Coghill et al. 1994; Hsieh 1995; Hsieh et al. 1994; Hsieh et al. 1995b; Hsieh et al. 1995d). The distinction accounts for the behavioural difference (opposite motor intention instigated in divergent hemisphere) of nocifensive approach (scratch) and avoidance (withdrawal) in acute itch and pain, respectively. Such contralateral engagement of BA24 in the confrontation of an acute pain facilitates in targeting premotor areas (SMA, PM and cingulate motor area) for initiating or inhibiting ('to not move' during functional imaging studies on experimentally induced acute pain) the protective motor behaviours (Devinsky et al. 1995; Hsieh 1995; Luppino et al. 1991; Pandya et al. 1981). As a contrast, the overt affectional/cognitive dimensions of sustained suffering of pain (provoked cluster headache,

chronic painful mononeuropathy and chronic painful trigeminal neuropathy) preferentially engages the right ACC. It is noteworthy that in the aforementioned study on brain electrical source analysis of laser evoked potentials in response to painful trigeminal nerve stimulation on the right face, the dipole IV (approximating BA24) was located in the left hemisphere while the dipole III (approximating BA 32/9) was identified in the right hemisphere (Broom and Chen 1995). The observed intricate and divergent patterns of central processing for different types of pain are in line with the current neuropsychological theories of hemispheric asymmetries in the limbic regulation of cognition (Liotti and Tucker 1995). Hemispheres are functionally lateralised according to different principles for cognitive/affective representation (Brown and Kosslyn 1993; Gainotti et al. 1993).

The provoked CH activated bilaterally the anterior insula (BA14, dorsal region), a pattern similar to that of chronic neuropathic pain (Hsieh et al. 1995a). The insula has been consistently demonstrated to be activated in pain imaging studies on experimentally induced pain. Anterior insula has more extensive connections with orbitofrontal, temporopolar, anterior cingulate, olfactory, gustatory, and autonomic structures whereas the posterior-dorsal insular is more closely connected to somesthetic, auditory, motor, and high-order association areas (Mesulam and Mufson 1985). This anterior region of insula has been activated by phobic anxiety (Drevets et al. 1995; Drevets et al. 1994) and transient sadness (Lane et al. 1995). The activation spatially extend to the middle insula, a region demonstrated to be involved in autonomic regulation (Minoshima et al. 1995). The activation here during CH attack with strong affect reflects a distributed processing of pain and is concurrent with the theory that the anterior portion of the insula is involved in affective processing, invest cognitive/interoceptive sensory stimuli with emotional significance, crucial in autonomic regulation, and is integral for conscious awareness of the self (Damasio 1993; Mesulam and Mufson 1985). Activation of the multiple foci in the primary motor area somatotopically reflects the observed intense tonic contraction (a physical strategy commonly employed by the patients to facilitate the alleviation of the CH attack, (Nappi and Russell 1993) of the corresponding face, upper and lower extremities. The SMA and the PM participate in these motor behaviours in response to CH (Hsieh et al. 1994; Rao et al. 1993). The lateral inferior frontal cortex (BA47) has been demonstrated to be bilaterally activated in chronic ongoing neuropathic pain (Hsieh et al. 1995a), possibly participates in normal emotional cognitive processes and regulation (Pardo et al. 1993). The activation of opercular cortex (BA44, 45) indicates internal/external vocalisation contingent upon the experience of outburst pain (Hsieh et al. 1995b).

As previously reported (Hsieh 1995; Hsieh et al. 1995c; Hsieh et al. 1996), multiple cerebral regions participating in other specialised neurocognitive functions, e.g., visuospatial and language processes (BA7,19,37,40) (Frackowiak 1994; Ghatan et al. 1995; Kawashima et al. 1995; Liotti et al. 1994) were inhibited during pain. It has been argued that the prefrontal cortex (PFC), especially the dorsolateral PFC, is essential for willed acts (Frith et al. 1991; Ingvar 1985) and that ACC involvement in behavioural control depends critically on a close interaction with the PFC (Hsieh et al. 1994; Paus et al. 1993; Porrino 1993). Bilateral deactivation in the PFC (BA 10) here may suggest a disengagement of the supervisory attentional system for cognitive planning (Cohen 1993; Hsieh et al. 1995d; Shallice 1982). Intense pain functionally inhibited these regions by virtue of its intrusiveness and fills the space of consciousness (Hsieh 1995; Price 1988).

The congruence between the observed temporal scenario of the tracer in the CS and the clinical profile supports the idea of a blood flow disturbance in the CS as part of the pathophysiology of CH. The time of investigation of PET was 100 sec following injection of [¹⁵O]butanol, a time sufficient to clear the CS off the radioactivity should the flow be normal (Greitz 1956). The increase of radioactivity in the CS after NTG and during CH attack indicates a longer transit time for the tracer in this region, which is equal to a lower perfusion (interpreted as impeded venous drainage in the CS). The rapid pain relief obtained with subcutaneous administration of sumatriptan was concurrent with the disappearance of the radioactive tracer. The decline of radioactivity in the CS, monitored in one of the NTG-negative cases (Fig. 2), during the post-NTG incubation period suggests a possibly normal regulating capacity of the cerebral hemodynamics in patients out of their cluster period. We previously indicated that the start of a CH attack could be due to an increase and the termination of the attack could be due to a decrease of flow in a sympathoplegic and phlebopathic CS (Hannerz et al. 1987; Hannerz and Jogestrand 1992; Hannerz and Jogestrand 1995). Accordingly, the pain during a CH attack would have its origin in the unilateral vasculitic CS (Hannerz et al. 1987; Hardebo and Moskowitz 1993). However, the limited time resolution of PET (80- to 100-sec scanning time) can only provide a hint to this. A way to solve this would be to carry out a study of quantitative flow (Greitz 1956). The markedly increased radioactivity in the nasal/paranasal sinus (Fig. 1) may have a bearing in the physical symptoms and signs of nasal congestion and rhinorrhea during the CH attack (IHS 1988).

In conclusion, our study indicates the preferential role of the right (non-dominant) hemisphere in processing the affective-cognitive dimensions of clinical pain syndromes. The ACC is one key to the experience of suffer-

ing of aversive pain (Devinsky et al. 1995; Hsieh et al. 1995a). The intricateness of the distributed central processing between provoked cluster headache attack and experimentally induced acute pain denotes different central mechanisms for different types of pain. This mode of analysis may provide hitherto unexplored functional neuroanatomical perspectives for pain and form a basis for further comprehensive research on central processing for various clinical pain syndromes.

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