

Website publication 17 February 1998

NeuroReport 9, 659–663 (1998)

A patient is presented who suffered a lateral brainstem infarction which selectively abolished pain and temperature sensitivity in the lower right limb. One year later central post-stroke pain had developed in the affected limb with touch and cold allodynia. P40m dipoles calculated from magnetoencephalographic fields after electrical stimulation of both tibial nerves were localized in SI as is seen in normal subjects. However, stimulation of the affected side caused deep pain sensations and elicited a large N80m component, best explained by an additionally active dipole in cingulate cortex. This early co-activation in a limbic structure suggests peripheral A $\beta$ -fiber mediation and lemniscal projection. Abnormal link to the pain system may be due to sensitization and reorganization above the level of nociceptive deafferentation.

**Key words:** Brainstem infarct; Central pain; Central plasticity; Cingulate cortex; Laser evoked potentials; Magnetoencephalography; Sensory function; Wallenberg's disease

## A $\beta$ -fiber mediated activation of cingulate cortex as correlate of central post-stroke pain

Jürgen Lorenz, Holger Kohlhoff, Hans-Christian Hansen,<sup>1</sup> Klaus Kunze<sup>1</sup> and Burkhart Bromm<sup>CA</sup>

Institute of Physiology and <sup>1</sup>Neurological Department, University Hospital Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany

<sup>CA</sup>Corresponding Author

### Introduction

Lesions within the central nervous system can cause so-called central pain which may develop after ischemic brain lesions, also referred to as central post-stroke pain (CPSP). Its prevalence was estimated as 1.5% of North American patients suffering a stroke<sup>1</sup> (cited from Ref. 2). In Wallenberg's disease there is an infarction of the posterior inferior cerebellary artery (PICA), a branch of the vertebral artery, which supplies neuronal structures of the lateral brainstem, including the spinothalamic tract, the descending spinal tracts of the trigeminal nerve, the central descending sympathetic tract and pontocerebellar pathways. Wallenberg's disease therefore involves contralesional loss of pain and temperature senses in trunk and limbs, ipsilesional loss of pain and temperature senses in the face, ipsilesional Horner's triad (miosis, ptosis, enophthalmus) and ipsilesional cerebellar ataxia. Medial brainstem structures, particularly the medial lemniscal tract, projecting sensory information related to touch, vibration and joint position typically remain intact in Wallenberg's disease. The presence of CPSP has been recently reported to be 25% in Wallenberg's disease,<sup>3</sup> indicating a clearly higher risk than in the overall stroke population. This fits the clinical findings that brain damages leading to deficits of pain and temperature sensitivity are more often associated with central pain than lesions affecting touch, vibration and joint position senses<sup>4,5</sup> (for review see Ref. 2).

We examined a patient with Wallenberg's disease both in the acute phase, 3 weeks after symptom onset, and one year later, during which CPSP had progressively developed. We applied evoked potential methods using brief nonpainful electrical and painful infrared laser stimuli. Previous work consistently showed that the combination of standard electrical somatosensory evoked potentials (SEP) and laser evoked potentials (LEP) can reliably verify the differential involvement of mechanoreceptive–lemniscal and nociceptive–spinothalamic deficits, respectively in a variety of pathologies including multiple sclerosis, syringomyelia, arteriovenous malformations and Wallenberg's disease.<sup>6,7</sup> In addition, source analysis of magnetic fields elicited by electrical tibial nerve stimulation of affected and nonaffected limbs was performed in the follow-up examination in order to study whether the unilateral development of CPSP had led to significant side differences of cortical lower limb representation.

### Materials and Methods

*Case report:* Upon hospitalization the 47-year-old male patient presented with typical symptoms and signs of a left lateral brain stem infarction: he had cerebellar hemiataxia and a Horner's syndrome on the left side, deficit for pain and temperature sensitivity on the right side of body and face whereas touch, vibration and joint position senses remained

intact. Although Wallenberg's disease typically exhibits the crossed pattern of dissociated sensory deficit (ipsilesional face and contralesional trunk and limb manifestation) the uncrossed pattern presented by this patient may occur if in case of a more ventral lesion the ascending postsynaptic spinal tract fibers of the trigeminal nerve instead of its descending presynaptic fibers are affected.<sup>8</sup>

T2-weighted magnetic resonance imaging (MRI) revealed a small left paramedian hyperintense zone at the floor of the IVth ventricle (Fig. 1). Digital subtraction angiography of the left vertebral artery delineated a segmental narrowing at its dural entry and a consistent failure to visualize the posterior inferior cerebellar artery (PICA). After anticoagulative treatment the patient's state markedly improved. Upon discharge cerebellar function had normalized. Pain and temperature sensitivity had almost fully recovered in the right arm and face, whereas the right lower limb was still analgesic and thermanaesthetic. Painful dysaesthesias developed during the hospital stay in the affected right leg and became increasingly severe within the 1 year of study. The pain was described as a deep, freezing, aching and very unpleasant sensation which occurred spontaneously

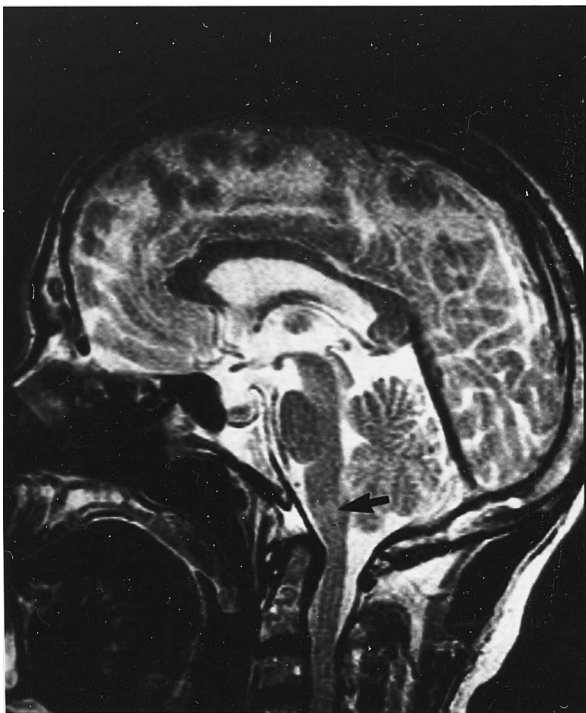


FIG. 1. T2-weighted magnetic resonance imaging (MRI) scan of the patient upon hospitalization about 48 h after symptom onset. The sagittal view in a left paramedian plane shows a small medullary ischemic lesion (see arrow). Three weeks later a repeated MRI scan confirmed this lesion, but with markedly smaller size.

every 2–3 h. In addition there was superficial allodynic pain elicited by light touch and cold stimuli, but not or clearly less by warm stimuli.

**Evoked potential recording:** SEP were recorded after transcutaneous electrical tibial nerve stimulation at the inner ankle (0.2 ms duration, 2 Hz repetition rate, 512 samples, intensity = sum of sensory and motor thresholds). LEP were elicited by CO<sub>2</sub>-laser stimuli (wavelength 10.6  $\mu$ m, 20 ms duration, 5 mm beam diameter, 40 samples) applied to the foot dorsum in a random sequence of 15 and 20 W intensities presented at variable intervals (10–20 s). Each side was tested twice in blocks with the following sequence: affected–unaffected–unaffected–affected. For SEP, EEG was recorded within 10–1000 Hz from an electrode placed over the foot area of the primary somatosensory cortex (SI; 2 cm behind Cz of the 10-20 system) using a frontal reference. For LEP, EEG was recorded within 0.5–70 Hz from Cz referenced against linked earlobes.

**Magnetoencephalography and dipole source analysis:** Somatosensory evoked magnetic fields (SEF) were recorded (0.3–1000 Hz) after electrical transcutaneous tibial nerve stimulation applied to both sides in the same way as described for SEP measurements. The cryostat (31 first-order axial gradiometers, Philips company) was centered over the respective SI areas (see above). At latencies of maxima in the global mean field power equivalent current dipoles (ECDs) were calculated within the patient's individual anatomy. Therefore, his head was modelled by a realistically shaped boundary element model (BEM) derived from the skin, outer and inner skull-surfaces, which were segmented from T1-weighted MRI (128 sagittal slices of 1.7 mm thickness) and which formed the three compartments of different conductivities. In addition, ECD locations were restricted to the individual gray matter which was also segmented from MRI (CURRY software, Philips).

## Results

Loss of LEP after stimulation of the right foot (Fig. 2, bottom left graph) in combination with preserved tibial nerve SEP (bottom right graph) 3 weeks after symptom onset confirmed the clinical diagnosis of a dissociated sensory loss in the lower right limb. Additionally, it was noted that SEP amplitudes from the affected side were generally higher than those from the unaffected side (top left graph). Most striking was the presence of a large negative component (N80) at the affected side which was only very small at the unaffected side. Recordings 1 year later (thick lines, see also Fig. 3) exhibited N80

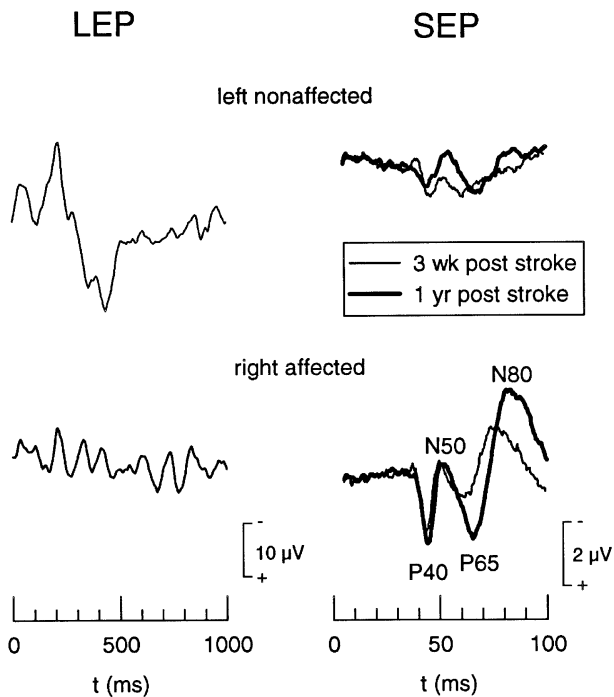


FIG. 2. Comparison of laser evoked potentials (LEP) after foot stimulation and standard electrical somatosensory evoked potentials (SEP) after transcutaneous tibial nerve stimulation. Pain sensitivity was selectively lost in the right lower limb which is confirmed by absence of LEP after right foot stimulation. SEP were elicited in both limbs as an indication that mechanosensitivity was preserved. It was however noted that SEP amplitudes were greater at the affected side. Upon re-examination 1 year later the P65/N80 was particularly further enlarged.

amplitude further augmented by about 100% compared with the recording 3 weeks after the stroke (thin lines). The P40 component did not change upon re-examination, yet the marked difference between both sides remained.

Reconstruction results of the equivalent current dipole (ECD) analysis within the individual MRI is illustrated in Fig. 4. The magnetic counterparts of P40, subsequently referred to as P40m, were best explained by single ECDs for both sides and were located in the primary somatosensory cortex (SI) of the postcentral gyrus contralateral to stimulation. In order to avoid mislocation of P40m, data were band-pass filtered at 10–500 Hz, previously described to be useful for early components.<sup>9</sup> One single ECD in right SI also explained N80m related to stimulation of the unaffected left tibial nerve. N80m after right (affected) tibial nerve stimulation, however, required two simultaneously active ECDs, one in SI and another in the posterior part of the cingulate cortex. All solutions explained 95–99% of the measured fields at the given time points.

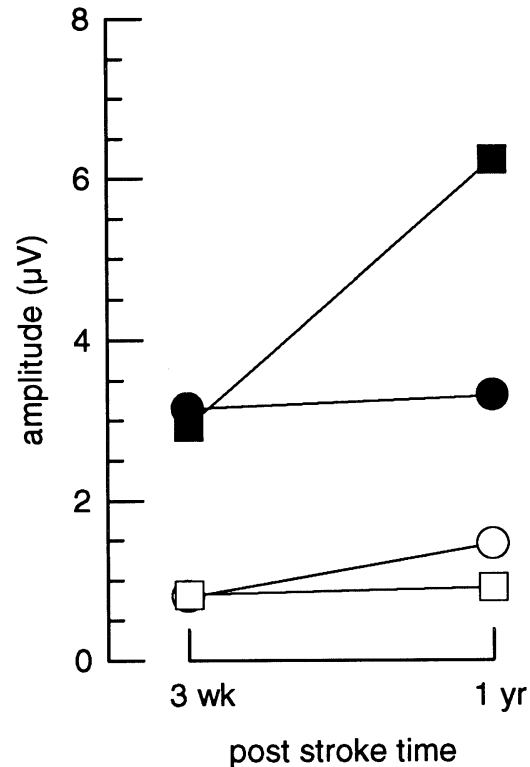
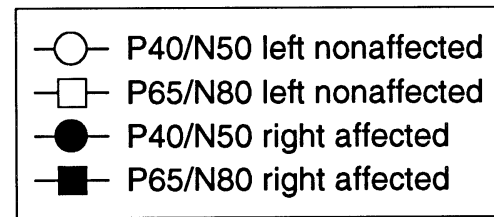
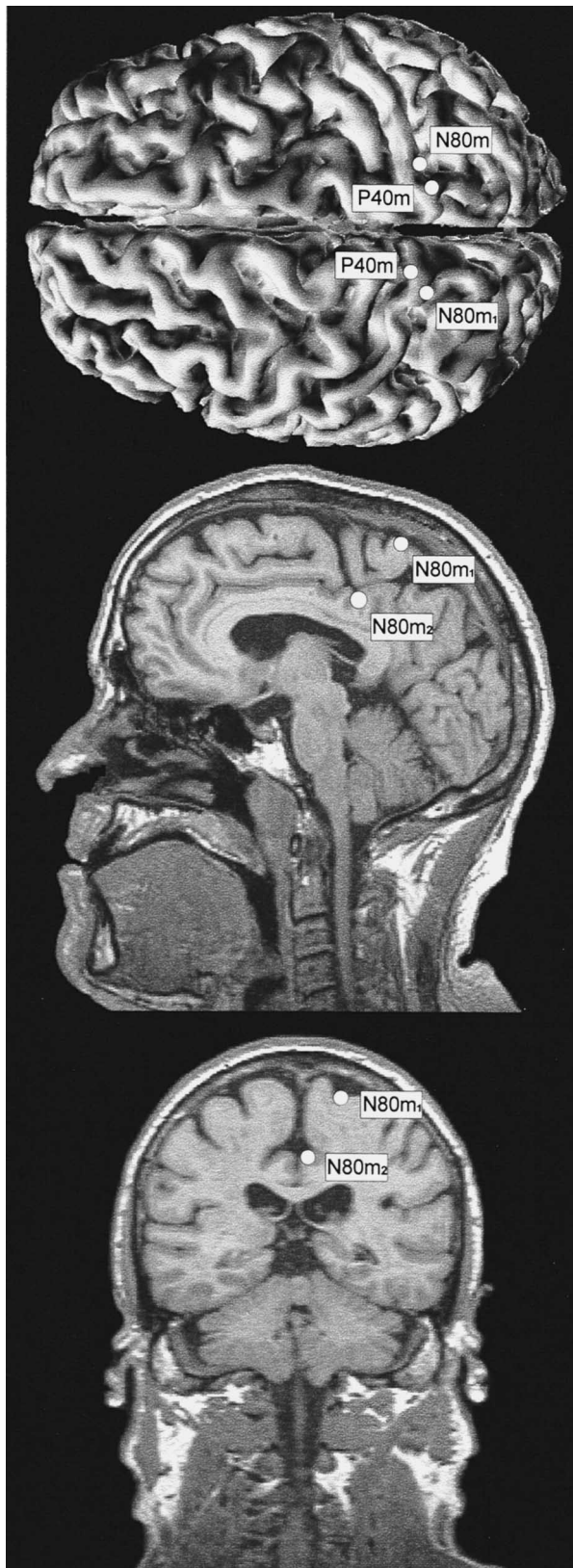


FIG. 3. Comparison of tibial nerve SEP amplitudes 3 weeks and 1 year after lateral brain stem infarction. Both P40/N50 and P65/N80 were larger after stimulation of the affected side in both sessions. However, only P65/N80 clearly augmented in the interval which correlated with the enhancement of clinical severity of central post stroke pain in the patient.

## Discussion

This study examined a patient who suffered a lateral brain stem infarction that had caused damage of the spinothalamic tract while sparing the medial lemniscal tract. This led to selective loss of nociceptive and thermoreceptive function. Central post-stroke pain (CPSP) started within the first weeks after symptom onset in the analgesic and thermanaesthetic right lower limb and became increasingly severe during 1 year of follow-up. Electrophysiologically, the affected right limb was characterized by larger components (P40 and N80) of the tibial nerve SEP compared with the nonaffected left limb. Particularly the enhanced N80 amplitude is regarded to relate to CPSP as this component augmented in parallel with the enhancement of CPSP severity in the patient.

after 1 year. Furthermore, source analysis of the magnetoencephalographic N80m component yielded different equivalent current dipole (ECD) localizations between both sides: whereas N80m from stimuli



applied to the nonaffected side exhibited an ECD located in SI of the contralateral postcentral gyrus, N80m from the affected side was best modelled by two dipoles, one in SI and another deeper in the posterior part of the cingulate cortex (CC). CC has been implicated by several authors to be involved in pain processing using brain electric source analysis,<sup>10,11</sup> positron emission tomography (PET)<sup>12-14</sup> and functional magnetic resonance imaging (fMRI).<sup>15</sup> CC activation was always described to accompany subjective sensation of pain. Also our patient reported aching deep pain sensations caused by the electrical stimuli. This is clearly abnormal when intensities slightly above motor threshold are used and there is strong evidence that it relates to CPSP in the patient, since both CC activation and pain were absent when stimulating the healthy side with comparable stimulus intensities.

Activation of CC mediated through peripheral A $\delta$ -nociceptors should be expected not earlier than 270 ms after foot stimulation based upon dipole source analysis of laser evoked potentials which consistently demonstrated CC activation coinciding with the major vertex negativity.<sup>10,11</sup> CC activation at about 80 ms after electrical foot stimulation is, therefore, clearly too early to result from transmission through slowly conducting nociceptive pathways. The findings in the patient rather suggest mediation by fast conducting A $\beta$ -fibers and projection via the medial lemniscal tract. The mechanisms by which activation of A $\beta$ -fiber low-threshold mechanoreceptors could lead to pain sensation as a consequence of stroke is unclear. It is known that A $\beta$ -fibers can signal allodynia and hyperalgesia after peripheral nerve injury,<sup>16,17</sup> probably on the basis of central sensitization at the dorsal horn or higher level in convergent, wide-dynamic-range (WDR) neurons. Input from the mechanoreceptive system to WDR neurons is obviously transferred as 'pain' only under pathological conditions. Activity-dependent plastic changes are known to occur after inflammation or nerve injury and can maintain a state of hypersensitivity (for review see Ref. 18). Not only dorsal horn but also thalamocortical projection neurons exhibit WDR properties<sup>19</sup> and can undergo plastic changes when disconnected from afferent input.<sup>20</sup> Thus, CPSP in our patient may be explained by deafferentation supersensitivity of thalamic projection neurons

FIG. 4. Dipole reconstruction results of magnetoencephalographic activities after tibial nerve stimulation of left nonaffected and right affected sides. P40m of both hemispheres and N80m of the right hemisphere were best explained by single equivalent current dipoles (ECDs) within the primary somatosensory cortex (SI) contralateral to stimulation. However, stimulation of the affected side yielded magnetic activity at about 80 ms poststimulus which required two simultaneously active ECDs, one (N80m1) in left SI and another (N80m2) in the cingulate cortex.

rendering an A $\beta$ -fiber mediated convergent input capable of producing pain. Craig *et al.*<sup>21,22</sup> suggested that the thalamus is important for integration of non-nociceptive and nociceptive input and that specific loss of nociceptive and thermoreceptive innervation of the ventral posterior thalamus in lesions of the spinothalamic tract could disinhibit the medial thalamic input to the CC.

We observed CC activation in our patient in the medial part, slightly more posterior than area 24 of the anterior CC which is most often regarded to be involved in pain processing (for review see Ref. 23). Differences among various pain studies concerning the rostro-caudal extension of CC activation may be related to methodological criteria. Whereas fMRI and PET measure slow metabolic reactions (in the range of seconds) to the stimulus, MEG and EEG are sensitive to the induced neuronal synchronization measured with high temporal resolution (in the range of milliseconds). Tonic pain, typically applied in fMRI and PET studies, might activate CC more rostrally than phasic pain, used in EEG and MEG studies. Reasons for such difference might be that tonic pain contains a generally stronger effective component than phasic pain. Furthermore, motor responses or their active withholding seem to be much more relevant with tonic than with phasic pain. Interestingly, Davis *et al.*<sup>24</sup> recently showed with fMRI that phasic electrical pain was localized more posterior in the CC than a 'tonic' attention task.

## References

1. Bonica JJ. Introduction: semantic, epidemiologic, and educational issues. In: Casey KL, ed. *Pain and Central Nervous Disease: The Central Pain Syndromes*. New York: Raven Press, 1991: 13-29.
2. Boivie J. Central pain. In: Wall PF and Melzack R, eds. *Textbook of Pain*, 3rd edn. New York: Churchill Livingstone, 1994: 871-902.
3. MacGowan DJL, Janal MN, Clark WC *et al.* *Neurology* **49**, 120-125 (1998).
4. Boivie J, Leijon G and Johansson I. *Pain* **37**, 173-185 (1989).
5. Casey KL, Beydoun A, Boivie J *et al.* *Pain* **64**, 485-491 (1996).
6. Bromm B, Frieling A and Lankers J. *Electroencephalogr Clin Neurophysiol* **80**, 284-291 (1991).
7. Hansen HC, Treede RD, Lorenz J *et al.* *J Clin Neurophysiol* **13**, 330-338 (1996).
8. Chia LG and Shen WC. *J Neurol* **240**, 462-467 (1993).
9. Buchner H, Waberski TD, Fuchs M *et al.* *Electroencephalogr Clin Neurophysiol* **100**, 332-342 (1996).
10. Tarkka IM and Treede RD. *J Clin Neurophysiol* **10**, 513-519 (1993).
11. Bromm B and Chen ACN. *Electroencephalogr Clin Neurophysiol* **95**, 14-26 (1995).
12. Jones AKP, Brown WD, Friston KJ *et al.* *Proc R Soc Lond B* **244**, 39-44 (1991).
13. Talbot JD, Marrett S, Evans AC *et al.* *Science* **251**, 1355-1358 (1991).
14. Coghill RC, Talbot JD, Evans AC *et al.* *J Neurosci* **14**, 4095-4108 (1994).
15. Davis KD, Wood ML, Crawley AP and Mikulis DJ. *Neuroreport* **7**, 321-325 (1995).
16. Lindblom U and Verillo VT. *J Neurol Neurosurg Psychiatr* **42**, 422-435 (1978).
17. Campbell JN, Raja SN, Meyer RA and Mackinnon SE. *Pain* **32**, 89-94 (1988).
18. Dubner R and Basbaum AI. Spinal dorsal horn plasticity following tissue or nerve injury. In: Wall PF and Melzack R, eds. *Textbook of Pain*, 3rd edn. New York: Churchill Livingstone, 1994: 225-241.
19. Kenshalo DR Jr, Giesler GJ, Leonard RB and Willis WD. *J Neurophysiol* **43**, 1594-1614 (1980).
20. Rausell E, Cusick CG, Taub E and Jones EG. *Proc Natl Acad Sci USA* **89**, 2571-2574 (1992).
21. Craig AD, Bushnell MC, Zhang ET and Blomquist A. *Nature* **372**, 770-773 (1994).
22. Craig AD, Reiman EM, Evans A and Bushnell MC. *Nature* **384**, 258-260 (1996).
23. Vogt BA, Sikes RW and Vogt LJ. Anterior cingulate cortex and medial pain system. In: Vogt BA and Gabriel M, eds. *Neurobiology of Cingulate Cortex and Limbic Thalamus*. Boston: Birkhauser, 1993: 313-344.
24. Davis KD, Taylor SJ, Crawley AP *et al.* *J Neurophysiol* **77**, 3370-3378 (1997).

ACKNOWLEDGEMENTS: The authors would like to thank Dr U. Grzyska for the MRI examination.

**Received 11 December 1997;**  
**accepted 23 December 1997**