PLASTIC INTERACTIONS BETWEEN HAND AND FACE CORTICAL REPRESENTATIONS IN PATIENTS WITH TRIGEMINAL NEURALGIA: A SOMATOSENSORY-EVOKED POTENTIALS STUDY

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Abstract—Neurophysiological and neuroimaging studies suggest that pain may play a major role in determining cortical somatosensory rearrangements even in the adult brain. The re-organizational power of pain, however, has been tested in models in which massive deafferentation co-existed with pain (e.g. in phantom pain). Moreover, information on whether spinal and brainstem changes contribute to pain-related plasticity in humans is meagre. We used the non-invasive somatosensory evoked potentials technique in patients with right primary trigeminal neuralgia and no clinical signs of large-diameter fibers of trigeminal deafferentation to assess whether pain may induce plastic changes at multiple levels in the somatosensory system. Subcortical and cortical potentials evoked by stimulation of the right median and posterior tibial nerves ipsilateral to the facial pain were compared with those obtained following stimulation of the left median and tibial nerves and with those obtained in a control group tested in comparable conditions. Amplitudes of peri-etal N20 and P27 and frontal N30 potentials observed following stimulation of the right median nerve ipsilateral to the facial pain were greater than those of the left median nerve and showed a positive correlation with magnitude of pain. This right–left asymmetry was absent following stimulation of the patients’ tibial nerves and in control subjects. No changes were found in spinal N13 and brainstem P14. That facial pain is associated with neuroplastic changes within the somatic cortical representation of the hand suggests a pain-related topographic cortical reorganisation. © 2004 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: pain, trigeminal neuralgia, somatosensory evoked potentials, SEPs, cortical plasticity, somatosensory system.

Intense noxious stimulation or tissue injury may bring about dramatic changes in sensitivity to both noxious and non-noxious stimulation as well as expansion of the receptive fields of dorsal horn neurones (Dougherty and Willis, 1992; Kenshalo et al., 1982; McMahon and Wall, 1984; Price et al., 1978; Simone et al., 1991; Woolf and King, 1990). Sensitization and expansion of receptive fields in response to inflammation and tissue injury or electrical nerve stimulation have been demonstrated also in the thalamus (Guilbaud et al., 1986) and somatosensory cortex (Lamour et al., 1983). The possible role of pain in promoting neuroplastic changes in humans has been suggested only recently. Magnetoencephalographic studies in amputee patients with phantom limb pain show that the amount of cortical reorganisation of the lower lip ipsilateral to the amputation is positively correlated with the magnitude of pain experienced by the subjects (Flor et al., 1995). Suppression of phantom pain contingent upon regional anesthesia is accompanied by a clear reduction of cortical representation of the lip ipsilateral to the amputation (Birbaumer et al., 1997) thus suggesting a tight link between pain and cortical reorganisation. In these models, however, pain co-existed with massive sensorimotor deafferentation, which also contributes to reorganisation. Recently, plastic changes of somatic representation induced by pain were reported in an experimental model of nociceptive pain in which acute pain induced by intradermal injection of capsaicin in the hand was associated with changes of magnetoencephalography (MEG) components evoked by stimulation of the lower lip ipsilateral to the injected hand (Soros et al., 2001). This suggests that acute nociceptive pain per se may induce rapid neuroplastic changes of somatic inputs coming from cutaneous territories with contiguous neural representations.

Here we report a neurophysiological study in which spinal, brainstem, and cortical somatosensory evoked potentials (SEPs) were recorded in patients with idiopathic right unilateral trigeminal neuralgia, a disorder of the fifth cranial (trigeminal) nerve that causes episodes of intense, stabbing, electric shock-like pain in areas of the face where the nerve branches are distributed. It is worth noting that paroxysmal pain in idiopathic trigeminal neuralgia seems to be primarily related to a dysfunction of Aβ afferents although minor involvement of myelinal Aδ fibers has been
demonstrated (Calvin et al., 1977; Cruccu et al., 1990, 2001, 2002; Devor et al., 2002).

The present research aims to: i) assess whether trigeminal pain may lead to reorganisation within the somatosensory pathway; ii) test whether neural remapping contingent upon trigeminal pain follows any topographic rules; iii) investigate at what level this modulation may occur. It is worth noting that, unlike magnetoencephalography, the SEP recording technique offers the unique opportunity to assess neural activity not only in different cortical somatosensory areas but also in cortical somatosensory areas and also in dorsal horn and dorsal columns from which the thalamus is innervated.

EXPERIMENTAL PROCEDURES

Subjects

We studied 10 right-handed patients (four women and six men), aged 49–68 years (mean 61) who complained for the first time of unilateral paroxysmal pain in the territory of mandibular, or mandibular (V3) and maxillary (V2) divisions of the right trigeminal nerve. In no patient was pain referred to the ophthalmic trigeminal division (V1). Relevant demographic and clinical information is provided in Table 1.

In all patients, the clinical picture was characterized by repetitive paroxysms of pain lasting a few seconds in the right V3 of the trigeminal nerve. In three subjects, pain also affected the territory of the right V2. Episodes occurred either spontaneously or when triggered by external stimuli. In eight patients, pain was elicited by delivering touch stimuli through Q-tips in the V3 division territory of the skin. Stimulation of the V2 division elicited pain in two patients. From a qualitative point of view, pain was described as electric shock-like, shooting or lancinating. Additional details on the characteristics and distribution of the trigeminal pain are provided in Table 1. Eight of the ten patients had undergone a brief period of treatment with non-steroid anti-inflammatory drugs and three patients with carbamazepine. All patients consented not to consume any drugs in the 72 h preceding SEP recording. In order to assess V3 division Aδ fiber function, trigeminal reflexes on each side of the face were recorded in all patients. In particular, ipsilateral and contralateral late components (R2 and R2c) of the blink reflex obtained by stimulation of the mental nerve were analyzed; also, the masseter inhibitory reflex was elicited by stimulation of the mental nerve and ipsilateral and contralateral first and second silent period were measured (Cruccu et al., 1989, 1990; Jaaskelainen, 1995; Ongerboer de Visser et al., 1990). In no patient did magnetic resonance imaging reveal the presence of structural lesions. Moreover, the absence of trigeminal reflex abnormalities and the clinical picture suggest that trigeminal neuralgia was not secondary to any known cause in any of the patients.

Subjective experience of facial pain was assessed by asking patients to rate the intensity of their neuralgia on a 10-point visual analog scale (VAS) where 0 corresponded to absence of pain and 10 to intolerable pain. Clinical examination of somatic function of the face was assessed by delivering series of brief, light touches on the right and left side of the face through Q-tips. Subjects were asked to report whether left- and right-sided stimuli had different intensity or quality. Trained neurologists who were unaware of the study aims carried out the clinical examination. No patient presented with clinical evidence of somatic deficits in the trigeminal neuralgia skin territory. Sensory stimuli delivered in the V3 and V2 skin territory often triggered paroxysmal pain in some subjects (see Table 1). Studies in normal subjects indicate that application of acute pain to the hand followed by non-noxious tactile stimulation of the ipsilateral lip produces phantom sensations on the hand in addition to the local sensation on the stimulated lip (Knecht et al., 1998). In view of this result, we assessed whether non-noxious stimulation of the hand evoked phantom-like sensations in the trigeminal pain territory. The thumb, index finger and thenar regions on the right side were stimulated by delivering 5 mm strokes on the skin by means of a Q-tip kept roughly perpendicular to the stimulated region. In addition, the right median nerve was stimulated electrically at motor threshold through skin electrodes over the wrist (interstimulus interval 5 s) for 3 min. Under both tactile and electric stimulation conditions, subjects were asked to report any anomalous sensations on the face in addition to the local sensation on the hand. Tactile and pain sensitivity in the hand region were also assessed in all subjects by means of electric stimuli delivered through ring electrodes positioned on the thumb on either the left or the right hand. The lowest intensity used in each subject was 1 mA. Series of stimuli with intensity increasing in steps of 0.1 mA were delivered. Subjects were requested to report whether or not they perceived any stimulation. The intensity value of the first stimulus perceived was adopted as a tactile threshold (TT) measure. After TT was measured, series of stimuli were delivered in which intensity increased in steps of 0.4 mA. In each trial, subjects were asked to report whether or not the stimulus was painful. The intensity value of the first stimulus perceived as painful was adopted as the pain threshold. The duration of each stimulus was 0.2 ms. The order in which thresholds were stimulated (left or right) was counterbalanced across the different subjects. Twelve right-handed healthy individuals (six women and six men) matched for age (range 27–65 years; mean 53.2) served as controls. All subjects were right-handed as ascer-

### Table 1. Clinical and demographic data of patients with right trigeminal neuralgia

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years)</th>
<th>Sex</th>
<th>VAS</th>
<th>Time since onset of pain (days)</th>
<th>Pain referred</th>
<th>Trigger referred</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>F</td>
<td>5</td>
<td>13</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>F</td>
<td>5</td>
<td>25</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>M</td>
<td>6</td>
<td>18</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>M</td>
<td>5</td>
<td>21</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>F</td>
<td>9</td>
<td>30</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>M</td>
<td>6</td>
<td>22</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>M</td>
<td>7</td>
<td>14</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>F</td>
<td>6</td>
<td>20</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>49</td>
<td>M</td>
<td>8</td>
<td>30</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>M</td>
<td>9</td>
<td>32</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*The presence of paroxysmal pain and trigger points in the maxillary or mandibular trigeminal division is marked by a plus sign (+, present; −, absent).
tained by the Oldfield Questionnaire (Oldfield, 1971). Written informed consent was obtained from all subjects. The procedures were approved by the institutional review board.

SEP recording procedure

During SEP recording sessions, subjects lay supine on a comfortable bed in a quiet room. SEPs were recorded by using an Esaote Biomedica Reporter (Esaote Biomedica, Florence, Italy).

Upper limb SEPs

For upper limb SEPs, recording electrodes (with impedance below 5 kΩ) were placed over the spinous process of the sixth cervical vertebra (Cv6) (referred to the anterior neck: AC), and in the parietal and frontal scalp regions contralateral to stimulation (P3, P4, and F3, F4) with an electrode reference located at the earlobe ipsilateral to the stimulation site. The bandpass was 5–1500 Hz (−3 dB at the cutoff point, 6 dB per octave) with an analysis time of 100 ms and a bin width of 103 μs. Stimuli were electrical square pulses of 0.2 ms duration delivered through skin electrodes over the median nerve at the wrist at a repetition rate of 1.8 Hz. The proximal electrode (cathode) was located 2 cm from the distal electrode (anode). The stimulus intensity was at the motor threshold and was comparable on the two sides in patients (right side: −5.1±1.1; left side: −5.2±1.3) and controls (right thumb: −5.3±1.1; left thumb: −5.1±0.9). Samples with an excess of interference were automatically rejected from the average. A total of 800 sweeps were averaged. Each test was repeated at least twice to confirm its reproducibility. Summed tracings of two repeatable averages were used for amplitude measurements (Tinazzi et al., 2000). To ensure full muscle relaxation, muscular activity was monitored through surface EMG recording from the flexor muscles of the arm on the stimulated side. The following components were identified: the N22 potential, recorded at Cv6 electrode, likely generated in the dorsal horn of the spinal cord (Desmedt and Cheron, 1981); this potential is preceded by the peripheral P9 far-field potential arising from the brachial plexus (Desmedt and Cheron, 1981); the far-field P14 potential recorded over the parietal and frontal electrodes, which originates from the cuneate nucleus (Desmedt and Cheron, 1981); the N20 and P27 potentials recorded over the parietal region contralateral to the stimulation side, which are thought to arise from area 3b (Allison et al., 1991; Desmedt et al., 1987; Valeriani et al., 2001a); the N30 potential, which is recorded over the parietal region contralateral to the stimulation side and at the vertex electrode, respectively. It is worth noting that both extracranial (Yamada et al., 1996; Baumgartner et al., 1998; Tinazzi et al., 1998b; Valeriani et al., 1997, 2000) and intracranial (Valeriani et al., 2001b) SEP recordings suggest that N37 arises from area 3b and P37 from area 1. The N50 potential, recorded over the vertex electrode, was also identified. Although the origin of this SEP component is still debated, studies suggest that it may be generated in area 1. The N50 potential is followed by the far-field P30 potential, recorded over the vertex electrode, and the P37 cortical potentials, recorded at the frontal electrode contralateral to the stimulation site and at the vertex electrode, respectively. It is believed that both extracranial (Yamada et al., 1996; Tinazzi et al., 1998b; Valeriani et al., 2000).

Analysis of SEP data

Amplitudes were measured from the preceding peak (peak-to-peak) for each SEP component. While within-group comparisons were performed on absolute amplitude SEP values, between-group comparisons were carried out on the side-to-side ratios of SEP components evoked by stimulation of the right (R) and the left side (L): R/L. It is worth noting that the ratio extraction procedure is recommended for reducing amplitude variability between individuals of different groups (Mauguieère and Desmedt, 1988).

Statistical analysis

Statistical analyses were carried out using non-parametric tests adept to control for possible violations of homogeneity of variance and effects of non-normal distributions. The unpaired Mann-Whitney test was used to compare tactile and pain sensitivity threshold values of the thumb and amplitude values obtained by stimulating median and posterior tibial nerves, on each side, in patients vs. controls. The paired Wilcoxon test was used to compare tactile and pain sensitivity threshold values of the thumb and SEP component values obtained by stimulation of the right median and posterior tibial nerves and those obtained by stimulation of the left median nerve, posterior tibial nerve, thumb and middle finger. The Spearman ranked-order correlation coefficient was used to assess possible relationships between: i) side-to-side ratio of amplitudes for the subcortical (spinal N13, brainstem P14) and cortical SEPs (parietal N20, P27, and frontal N30); and ii) side-to-side amplitude ratio of each SEP component with scores obtained using the VAS. The α level for significance was set at P<0.05. It is worth noting that correlation analysis may suffer from the comparatively small data sample and thus be much too conservative. Values in the text, tables and figures are given in the form of mean (±S.E.).

RESULTS

No patients reported any phantom sensations during spontaneous or triggered trigeminal pain. In addition, no patients reported tactile or phantom pain sensations in the trigeminal pain territory when tactile or electrical non-noxious stimuli were delivered on the ipsilateral hand. It is
worth noting that no patients reported paroxysmal trigeminal pain during SEP recording.

TT measures (mean±S.D. in mA) in the region of the thumb were not different (P>0.05) in patients (right thumb=3.3±0.6; left thumb=3.0±0.6) and controls (right thumb=3.1±0.5). Moreover, pain threshold in the region of the thumb was comparable (P>0.05) in patients (right thumb=21.0±3.7, left thumb=21.4±3.2; left thumb=21.1±3.5).

**Neurophysiological findings**

Mean amplitudes (±S.E.) for the different median nerve SEP components in patients and controls are reported in Table 2.

It appears that stimulation of the patients’ right median nerve ipsilateral to the facial pain evoked cortical N20, P27, and N30 potentials with significantly larger amplitudes than those evoked by stimulation of the left median nerve (P<0.05).

The pattern of SEP components from a representative patient (Fig. 1) indicates that right-left asymmetry of cortical potentials can be detected even at the single subjects’ level.

By contrast, no significant right-left differences were observed for spinal N13 and brainstem P14 potentials. No right-left asymmetry was observed in patients after stimulation of the tibial nerve (Table 3).

In the control group, there were no right–left differences in SEP components evoked by stimulation of the median and tibial nerve (P>0.05). It is relevant that the P9 and the P17 originating from brachial and lumbar plexus respectively were not different in patients and controls. This suggests that the magnitude of the signal delivered to and entering the CNS was similar in patients and normal subjects.

**Right–left amplitude ratio of SEP components**

Fig. 2 reports the right-to-left amplitude ratio of the different central SEP components evoked by stimulation of the

<table>
<thead>
<tr>
<th>SEP component</th>
<th>Patients</th>
<th>Controls</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>N13</td>
<td>1.29±0.15</td>
<td>1.31±0.19</td>
</tr>
<tr>
<td>P14</td>
<td>0.83±0.13</td>
<td>0.80±0.10</td>
</tr>
<tr>
<td>N20</td>
<td>2.95±0.34</td>
<td>2.08±0.23</td>
</tr>
<tr>
<td>P27</td>
<td>3.53±0.39</td>
<td>2.56±0.32</td>
</tr>
<tr>
<td>N30</td>
<td>3.44±0.32</td>
<td>2.47±0.30</td>
</tr>
</tbody>
</table>

*The values of significant, right–left comparisons are in boldface.

### Table 3. Mean (±S.E.M.) amplitude values (in μV) of the subcortical and cortical SEP components obtained in response to stimulation of the tibial nerves in the experimental groups

<table>
<thead>
<tr>
<th>SEP component</th>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>N22</td>
<td>0.36±0.04</td>
<td>0.34±0.03</td>
</tr>
<tr>
<td>P30</td>
<td>0.60±0.08</td>
<td>0.54±0.06</td>
</tr>
<tr>
<td>N37</td>
<td>1.21±0.13</td>
<td>1.09±0.12</td>
</tr>
<tr>
<td>P37</td>
<td>1.37±0.13</td>
<td>1.32±0.14</td>
</tr>
<tr>
<td>N50</td>
<td>2.50±0.26</td>
<td>2.26±0.17</td>
</tr>
</tbody>
</table>

The pattern of SEP components from a representative patient (Fig. 1) indicates that right-left asymmetry of cortical potentials can be detected even at the single subjects’ level.

By contrast, no significant right-left differences were observed for spinal N13 and brainstem P14 potentials. No right-left asymmetry was observed in patients after stimulation of the tibial nerve (Table 3).

In the control group, there were no right–left differences in SEP components evoked by stimulation of the median and tibial nerve (P>0.05). It is relevant that the P9 and the P17 originating from brachial and lumbar plexus respectively were not different in patients and controls. This suggests that the magnitude of the signal delivered to and entering the CNS was similar in patients and normal subjects.

**Fig. 1.** SEPs to right and left stimulation of the median and tibial nerves in a representative patient (Table 1, patient 10). The amplitudes of cortical potentials N20, P27 and N30 obtained by stimulation of the right median nerve (ipsilateral to the side of facial pain) are greater than those obtained by stimulation of the left median nerve. By contrast, no modulation of the peripheral P9, spinal N13 and brainstem P14 potentials was found. It is relevant that no asymmetry of cortical SEP amplitude was detected following stimulation of the right and left tibial nerves.
median (upper part) or the tibial (lower part) nerves in patients and controls. The mean right-to-left amplitude ratio of all cortical SEP components (N20, P27, N30) obtained by stimulation of the median nerve were significantly greater in patients than in controls (Mann-Whitney test, \( P < 0.05 \)). By contrast, patients and controls did not show any difference in the right-to-left ratio for the subcortical components (N13 and P14). The right-to-left ratio of the peripheral P9 component was not different in patients and controls thus indicating that the increased electrical activity in the patients' somatosensory pathway originated at a central rather than a peripheral level. No significant differences in SEP amplitudes were observed between patients and control subjects when the tibial nerve was stimulated (Fig. 2, lower part).

Correlation analyses

No significant correlation between differences in amplitude of subcortical (spinal N13 and brainstem P14) and cortical (N20, P27, and N30) potentials evoked by stimulation of the right median nerve was observed. This result suggests that the enhancement of the cortical response is largely independent from any enhancement of spinal and brainstem components.

Reports of subjective intensity of pain during a typical episode of trigeminal neuralgia are shown in Table 1. These data were used for correlation analyses with amplitude of the different SEP components. No significant correlation between right–left amplitude ratio of cortical SEP components and magnitude of pain as inferred from VAS scores (for N20 \( r = 0.33; \) \( P = 0.26 \); for P27 \( r = 0.59; \) \( P = 0.056 \); for N30 \( r = 0.47, \) \( P = 0.12 \)) was found. Moreover, no correlation between amplitude of SEP components with duration of pain and tactile and pain sensitivity was observed (\( P > 0.05 \)).

**DISCUSSION**

The main result of the present study on patients with idiopathic right-sided trigeminal neuralgia is that cortical potentials evoked by stimulation of the median nerve ipsilateral to the side of facial pain were higher than those evoked by stimulation of the median nerve contralateral to the side of facial pain. No right–left asymmetry was found in amplitude of potentials evoked by stimulation of the tibial nerve in the patient group. Moreover, no asymmetry whatsoever was detected in control subjects.

**Pain-related neuroplasticity in the somatic system**

Acute or chronic pain in humans may induce neuromodulation changes within the nociceptive system (Iadarola et al., 1998; Lenz et al., 2000; Olausson et al., 2001; Valeriani et al., 2003). The application of capsaicin to a given body part, for example, induces a decrease in the amplitude of CO2 laser potentials evoked by stimulation of cutaneous zones of primary and secondary hyperalgesia. This indicates that painful stimuli delivered to a given nociceptive channel bring about a decrease in activity in adjacent nociceptive channels (Valeriani et al., 2003).

Studies also show that pain can induce neuromodulation effects across channels dedicated to different somatic modalities such as touch (Birbaumer et al., 1997; Flor et al., 1995, 1997; Juottonen et al., 2002; Tinazzi et al., 2000). Some studies of pain-related plasticity involving the somatic system, however, have been carried out in limb amputee subjects in whom modulation of cortical somatic areas representing skin territories contiguous with painful regions was found (Birbaumer et al., 1997; Flor et al., 1995). Although phantom pain co-existed with a massive deafferentation of large-diameter fibers, which is known to promote neuromodulation changes per se, all these studies converge to indicate that pain plays an important role in promoting cortical somatic reorganisation (Birbaumer et al., 1997; Flor et al., 1995). Moreover, studies suggest that fairly complex interactions regulate neuromodulation phenomena in conditions in which pain and deafferentation coexist (Rosso et al., 2003).

Thus, it is important to emphasize that a crucial role of pain in promoting reorganisation changes of somatic representations such as touch has been demonstrated in...
normal subjects (Soros et al., 2001) and in patients with no deafferentation of large-diameter fibers (Tinazzi et al., 2000). Relevant to this issue is our previous study in patients who complained of pain in the right thumb following a right cervical monoradiculopathy due to compression of the sixth cervical root (Tinazzi et al., 2000). Despite the absence of signs of large-fiber deafferentation, SEP amplitudes recorded in response to stimulation of the painful thumb were greater in these patients than SEP amplitudes recorded in response to stimulation of the non-painful left thumb and were related to pain intensity. Moreover, no change in SEP amplitude was found following stimulation of the right (non-painful) middle finger thus indicating that the increased excitability of somatosensory structures was specific to the painful region (Tinazzi et al., 2000). Paroxysmal pain never occurred during SEP recording in any of the patients in this study. Therefore, another novel result is that plastic effects of pain on the somatosensory system can be observed outside the painful episode and therefore are not only linked to ongoing noxious stimulation. This is in keeping with studies showing long-lasting peripheral and central changes following noxious stimulation (Gracely et al., 1992).

In the present study, changes in the amplitude of potentials evoked by stimulation of the median nerve ipsilateral to the side of neuralgia were likely due to pain pathways not only because they were absent in control subjects but also because the finding of normal trigeminal reflexes in patients suggests the absence of any major Aβ fiber deafferentation (Crucu et al., 1989, 1991).

Another point deserving discussion concerns the possible presence of referred sensations induced by acute pain. Knecht et al. (1998) induced acute pain in the hand region of healthy subjects by intradermal injections of capsaicin. Non-noxious tactile stimulation of the lip ipsilateral to the side of the pain evoked phantom-like sensations on these subjects’ hands synchronous to the lip stimulation. This has been interpreted as the perceptual correlate of the activity of unmasked silent connections between neural regions mapping hand and lip. In view of this result, we assessed whether tactile stimulation of the hand could elicit double sensations on the face. No phantom pain or tactile sensations were elicited in patients with trigeminal neuralgia. Although speculative, a possible explanation for this negative result is that patients were not tested during episodes of paroxysmal pain.

**Topography of plasticity across pain and tactile channels**

In patients with trigeminal pain, but not in controls, cortical SEPs obtained by stimulation of the median nerve ipsilateral to facial pain were greater than those obtained from the contralateral hand. Moreover, this side-to-side asymmetry was not found following stimulation of the leg ipsilateral to the side of neuralgia. Thus, the pain-related increase in excitability of cortical somatic structures was extended to skin territories with neighboring representations indicating that plastic changes can occur across representations mapping different somatic inputs coming from adjacent skin territories. This is in keeping with a MEG study in patients with low back pain in whom a strong correlation between shifts in the cortical position of the magnetic dipole evoked by somatic stimulation of the painful territory and the magnitude of pain was found (Flor et al., 1997). Interestingly, although the cortical representation of the back was shifted toward the foot area, no changes in the representation of the hand were observed. This result suggests a somatotopic pattern of remapping contingent upon ongoing noxious input from the painful region (Flor et al., 1997). It seems that the most direct way of addressing the issue of somatic plasticity contingent upon trigeminal pain is to record potentials evoked by stimulation of the face territory. Unfortunately, however, there is no reliable evidence that specific SEP responses reflecting cortical neural activity of the trigeminal territory can be recorded over the scalp (Leandri et al., 1989). Thus, although somewhat indirect, the finding that trigeminal pain induces plastic changes across different somatic modalities subserving skin territories with contiguous neural representation expands our previous study on plasticity across pain and somatic channels in patients with cervical compression (Tinazzi et al., 2000). In the present study, changes in amplitude are reported for N20, P27 and N30 potentials; thus, the suggestion is made that plastic phenomena contingent upon facial pain occur in different somatic areas. Indeed, the N20 and P27 potentials likely originate from area 3b (Allison et al., 1991; Desmedt et al., 1987; Valeriani et al., 2001a) and the N30 potential, recorded over the contralateral frontal region, originates from multiple generators located either in the frontal lobe or in the posterior wall of the central sulcus (Allison et al., 1991; Desmedt et al., 1987; Mauguie`re et al., 1983).

**Cortical and subcortical loci of remapping**

Studies on animal (Florence and Kaas, 1995; Pettit and Schwark, 1993) and human (Tinazzi et al., 1997, 1998a, 2000) models show that changes contingent upon a decrease or an increase of sensory input occur not only at cortical but also at brainstem and thalamic levels of the somatic system (Florence et al., 2000; Jain et al., 2000). In the present study, pain-related modulation of somatosensory activity involved only cortical SEP components thus indicating that changes in excitability in the primary somatic cortex seem to occur independently from changes upstream in the sensory pathway. Although direct recordings of neural activity suggest that thalamic structures significantly modulate pain-related cortical changes (Davis et al., 1998; Guilbaud et al., 1986; Katz et al., 1999), the present study cannot provide information on this issue because there is no reliable evidence that SEP components reflecting specific neural activity in the somatosensory thalamus can be recorded over the scalp.

The absence of modulation of subcortical components N13 (which reflects post-synaptic neuronal activity of the dorsal horn) and P14 (which reflects postsynaptic response of the nucleus cuneate) found in the present study cannot be ascribed to intrinsic limitations of the SEP technique. Indeed, plastic changes of SEP components at
multiple levels of the somatosensory system have been demonstrated in patients with carpal tunnel syndrome (Tinazzi et al., 1998a) and cervical radicular pain (Tinazzi et al., 2000). Thus, a possible explanation for the lack of pain-related modulation of subcortical SEP components is that somatic and pain afferents from the face and hand are sent to the CNS through completely separate nerves and are represented in largely separate brainstem–spinal cord structures (DaSilva et al., 2002; Sessle, 2000). Moreover, no convergence of cutaneous afferents coming from trigeminal and hand territories within dorsal horn and nucleus cuneatus has ever been reported. In conclusion, our study extends current knowledge of the neuroplastic effects of trigeminal pain by showing that it may influence not only the nociceptive but also the somatic system.

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M. Tinazzi et al. / Neuroscience 127 (2004) 769–776 775

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REFERENCES


