Cutaneous Painful Laser Stimuli Evoke Responses Recorded Directly From Primary Somatosensory Cortex in Awake Humans

S. Ohara, N. E. Crone, N. Weiss, R.-D. Treede, and F. A. Lenz

Departments of Neurosurgery and Neurology, Johns Hopkins Hospital, Baltimore, Maryland 21278; and Institute of Physiology and Pathophysiology, Johannes Gutenberg University, D-55099 Mainz, Germany

Submitted 22 September 2003; accepted in final form 29 October 2003

Cutaneous painful laser stimuli evoke responses recorded directly from primary somatosensory cortex in awake humans. J Neurophysiol 91: 2734–2746, 2004. First published November 5, 2003; 10.1152/jn.00912.2003. Negative and positive laser evoked potential (LEP) peaks (N2*, P2**) were simultaneously recorded from the primary somatosensory (SI), parietal, and medial frontal (MF) cortices through subdural electrodes implanted for the surgical treatment of intractable epilepsy. Distribution of the LEP N2* and P2** peaks was estimated to be in cortical areas (SI, parietal, and MF) identified by anatomic criteria, by their response to innocuous vibratory stimulation of a finger (v-SEP), and to electrical stimulation of the median nerve (e-SEP). The maximum of the LEP N2* peak was located on the CS, medial (dorsal) to the finger motor area, as determined by cortical stimulation, and to the finger somatosensory area, as determined from the e-SEP and v-SEP. This finding suggests that the generator source of the LEP N2* peak in SI was different from that of e-SEP or v-SEP in Brodmann’s areas 3b or 1. In parietal and MF, polarity reversal was often observed, indicating tangential current sources in these regions. In contrast to e-SEP and v-SEP, the LEP N2* latency over SI was not shorter than that over the parietal region. The amplitude of N2* was larger over SI than over MF and the latencies of the LEP peaks in those 2 regions were different. These findings provide evidence for a significant LEP generator in the postcentral gyrus, perhaps SI cortex, that is situated outside the parietal cortex and receives its input arising from nociceptors simultaneously with parasympathetic and MF cortex.

INTRODUCTION

Our understanding of cortical pain mechanisms has been revolutionized by the evidence of imaging studies, in which painful stimuli have often failed to activate the primary somatosensory cortex (SI) (Derbyshire et al. 1994, 1998; Iadarola et al. 1998; Jones et al. 1991; May et al. 1998; Paulson et al. 1998). Recently, SI has been activated in imaging studies using paradigms that modulate the perceived intensity of the painful stimulus (Bushnell et al. 1999; Hofbauer et al. 2001) and in those that use newer analytical methods (Petrovic et al. 2002).

Electrophysiological studies in humans have often observed no SI cortical response to painful stimuli. For example, many laser-evoked potential (LEP) studies and some magnetoencephalographic [MEG; laser-evoked field (LEF)] studies have failed to detect an SI generator (Bromm and Chen 1995; Bromm et al. 1996; Huttunen et al. 1986; Kakigi et al. 1995; Valeriani et al. 1996, 2000). However, other LEP studies (Kanda et al. 2000; Kunde and Treede 1993; Spiegel et al. 1996; Tarkka and Treede 1993; Treede et al. 1988; Xu et al. 1995) and some recent LEP studies have identified a generator in the SI region (Kanda et al. 2000; Ploner et al. 1999, 2000, 2002; Schlereth et al. 2003; Timmermann et al. 2001).

Our previous studies have demonstrated that cortical potentials can be recorded independently from electrodes implanted over medial frontal cortex (MF) (Lenz et al. 1998b) and parietal cortex (Lenz et al. 1998a) anterior to primary auditory cortex at the junction of the parietal operculum and the insula (Lenz et al. 2000; Vogel et al. 2003). We now present the results of subdural cortical LEP recording in patients who underwent implantation of subdural electrodes over SI, parietal, and MF cortex for surgical treatment of intractable epilepsy. The results demonstrate that subdural LEPs can be simultaneously recorded from the cortical surfaces of these 3 anatomically distinct areas. The generator of LEPs recorded over the high convexity was estimated to be in SI by comparison of the location of these LEPs with that of reliable landmarks of the primary sensory and motor cortices.

METHODS

Subjects

These studies were carried out in 4 patients (3 female, 1 male, ages 21–51 yr at the time of surgery) who had subdural grids implanted for surgical treatment of medically intractable seizures. Subdural electrode grids were implanted over the left lateral frontoparietal area (Patient 1, Figs. 3–6), right lateral convexity and medial frontoparietal area (Patient 2, Figs. 1, 2, and 5), and left lateral frontoparietal convexity and medial frontoparietal area (Patients 3 and 4, Figs. 3–6). Neurological examination, including a standard sensory testing protocol (Lenz et al. 1993), disclosed no abnormality in any patient. Brain magnetic resonance imaging (MRI) revealed bilateral subcortical T2 changes consistent with enlarged perivascular spaces (Adams et al. 1996) (Patient 2) and a small cavernoma in the right parietal lobe (cortical to the side of implantation, Patient 4). All studies were carried out at the Johns Hopkins Hospital in 2002–2003. The protocol was approved by the Institutional Review Board of the Johns Hopkins University and all patients signed an informed consent for these studies.

LEP studies

Patients wore protective glasses throughout testing and lay on a bed with their eyes open, quietly alert. Cutaneous heat stimulation was...
delivered with a portable Thulium YAG laser (wavelength 2 μm, duration 1 ms; Wavelight, Starnberg, Germany). A laser beam of approximately 6 mm diameter was applied to the dorsum of the hand contralateral to the site of implantation. To avoid sensitization, the laser beam was moved randomly to a slightly different position for each stimulus. Before recording, laser pulses with different energy levels (from approximately 300 to 800 mJ) were given to the subjects. Subjects were asked to rate pain intensity using a scale from 0 to 10 (0, no pain; 10, most intense pain imaginable). In the case of Patient 1, we chose 3 different energy levels (400, 600, and 800 mJ), which generated painful sensations with the intensity of approximately 1, 2–3, and 3–4/10, respectively. A total of 60 laser pulses, 20 for each energy level, were randomly applied during each session with interstimulus interval (ISI) of 7–11 s. Sessions were repeated with ISI of 10 s. Two sessions were recorded with the interval of 1–2 min. In the present study, we analyzed evoked responses only to 800-mJ laser pulses (Patient 1). We chose a laser energy level for each of Patients 2–4 so as to generate painful sensation of 3–4/10 to correct for individual variability in pain sensitivity. A total of 40 laser pulses with a fixed energy level (560 mJ for Patient 2, 720 mJ for Patients 3 and 4) were delivered randomly with ISI of 5–10 s. Two sessions were recorded with the interval of 1–2 min. Patient 1 was asked to rate pain intensity after each laser pulse. Patients 2–4 were asked to count the number of laser pulses silently and report the number of laser pulses and the average pain intensity after each session, to maximize the size of the potential by directing attention to the stimulus (Beydoun et al. 1993, 1997; Garcia-Larrea et al. 1997; Legrain et al. 2002; Siedenberg and Treede 1996; Zaslansky et al. 1996).

e-SEP

e-SEPs were recorded by electrically stimulating the median nerve at the wrist contralateral to the side of the implantation with ISI of 213 ms. The duration of electric pulse was 300 μs and the intensity was set at approximately 15–20% above the motor threshold for the abductor pollicis brevis muscle.

v-SEP

v-SEPs were recorded for Patients 2–4 (Figs. 1, 2, and 3, B and C). Vibrotactile stimuli were generated with a computer-controlled Chubbuck mechanical, cutaneous, stimulator (Chubbuck 1966) applied to the palmar surface of the distal phalanx of the index finger, contralateral to the grid. The tip of the stimulator probe was round (diameter of 3 mm) and was placed on the skin with a force of approximately 50–100 g. A 120-Hz vibration with duration of 100 ms and with amplitude of 100 μm was superimposed on this baseline force, likely activating Pacinian receptors (Mountcastle 1984). For each run, approximately 200 vibratory stimuli were applied to the index finger with ISI of 3 s. At least 2 runs were obtained.

Data acquisition

Cortical electrical activities were recorded from subdural grid electrodes [electrocorticogram (ECoG)]. The electrodes consisted of platinum–iridium circular electrodes (2.3 mm diameter) embedded in a transparent silastic sheet at evenly spaced 1-cm center-to-center intervals (Ad-Tech, Racine, WI). ECoG from subdural grid electrodes ≤96 channels were amplified and band-pass filtered at 0.1–300 Hz for LEP and v-SEP, and 30–300 Hz for e-SEP with Grass amplifiers (12A5, Astro-Med, West Warwick, RI). All ECoG signals were referenced to a single intracranial (subdural) reference electrode chosen for its inactivity and distance from the active electrodes. The amplified ECoG signals were digitized at 1,000 to 2,500 Hz and recorded to computer hard disk along with stimulus markers for subsequent off-line analysis.

Anatomical correlation of cortical functions

Sensory, motor, and language functions were mapped by means of cortical stimulation and recording of e-SEPs, as described elsewhere (Lenz et al. 1998a,b; Lesser et al. 1992; Luders et al. 1987). Briefly, pulses of duration 0.3 ms and alternating polarity at 50 pulses/s were applied across pairs of adjacent electrodes in trains of 2–5 s duration. This technique produced excitation both of the stimulated electrodes in a pair (Randck Jr 1975). The electrode pairs (bipolar stimulation) or electrodes (monopolar stimulation), where hand and/or finger positive motor response was evoked by stimulation, were shown in each figure by gray oval or round areas, respectively (hand/finger positive motor area).

The positions of subdural electrodes over the convexity were determined relative to the central sulcus (CS) and the Sylvian fissure (SF) by e-SEP N20-P20 polarity reversal, intraoperative observation and photographs, and perioperative radiological studies including superimposition (3D CT-MRI) of 3D postoperative computed tomography (CT) on 3D preoperative MRI data sets, as in previous studies (Boatman et al. 1997; Crone et al. 1998; Lenz et al. 1998a,b). e-SEP N20-P20 polarity reversal (CSE) and intraoperative pictures were consistent in terms of CS location in 3 patients who had intraoperative pictures available (Patients 2–4). SF location based on intraoperative picture was consistent with 3D CT-MRI data in Patient 4. In Patients 2 and 3, SF was not clearly visible in intraoperative pictures, so location of SF was based on sulcal anatomy of the convexity as estimated by e-SEP and 3D CT-MRI. The sulcal anatomy based on 3D CT-MRI data were then used to make diagrams of the cortical surface (see figures). The locations of e-SEP N20-P20 polarity reversal (dotted lines) and of the N20 maximum (arrowheads) are also shown in each figure.

The positions of subdural electrodes on the interhemispheric surface were determined by superimposition of midsagittal plane of the preoperative T1-weighted MRI and the lateral view of skull X-ray taken after implantation of grids for Patients 2 and 3 (Ikeda et al. 1995, 1996; Ohara et al. 2000a,b). For Patient 4, we used the midsagittal plane of postoperative 3D CT instead of lateral view of skull X-ray.

Data analysis

Multichannel ECoG signals were remanaged using an average reference to minimize the influence of location and activity of the reference electrode (Crone et al. 1998; Lehmann 1987). ECoGs were averaged time-locked to the onset of laser pulse for LEP, of vibratory stimulation for v-SEP and of median nerve stimulation for e-SEP. A time window of 0.6 s with 0.1-s prestimulus period was used for LEPs and v-SEPs and a time window of 120 ms with 20-ms prestimulus period for e-SEPs. Responses to individual laser pulse and vibratory stimuli were reviewed and trials with artifacts or large baseline fluctuation were excluded before averaging. No artifact rejection was performed for e-SEP. For each subject, averaged waveforms were obtained after confirming the reproducibility of results from 2 recording sessions. A total of 30–76 responses for LEP, 142–220 for v-SEP, and 2,018–5,200 for e-SEP from 2 sessions were used for averaging.

Peak latencies and amplitudes were measured from reproducible, averaged waveforms. Peak amplitudes were measured from the baseline value, which was defined as the averaged value during the prestimulus period. All latencies were measured as the time of the peak amplitude for each component. Peaks were regarded as significant when the peak amplitude was above the mean + 2 SD prestimulus level.

In describing LEPs, we referred to the large, single, mostly negative wave as N2* and to the large, single, mostly positive wave following N2*, as P2**. As described in the Discussion section (Methodological considerations), the latencies of subdural LEPs differed from those of scalp recorded LEPs (Beydoun et al. 1993; Chen and Bromm 1995; Kitauma et al. 1995; Kunde and Treede 1993; Tarkka and Treede 1993). To emphasize this difference, we placed asterisks after the conventional abbreviations N2 and P2, and used the asterisks to mark these same potentials in the figures. The risk of wound infections precluded simultaneous subdural and scalp recordings.
We often observed polarity reversal of those peaks across a major sulcus, such as CS. We analyzed the first significant peak in each region for v-SEP, and N20-P20 and P25 components for e-SEP. To make distribution maps of peak amplitude, the amplitude during 10 ms around the peak latency of the maximum (5 ms before and after) was averaged for each electrode for each peak of LEP, and during 4 ms around the peak latency of the maximum for v-SEP peaks in each region. For e-SEP, only the value at the peak was analyzed. The peak amplitude was then plotted using circles with different diameters as a function of amplitude (Figs. 2 to 6).

To address the amplitude difference between regions, the mean LEP N2* and P2** amplitudes were calculated from amplitudes of all sites with significant N2* or P2** peaks where the amplitude exceeded 25% of the maximum. These amplitudes were then compared between regions (SI, parasylvian region, and MF) by a one-way ANOVA followed by post hoc analysis with Tukey’s honestly significant difference (HSD) for multiple comparisons.

The location of the maximum of the LEP N2* and P2**, e-SEP P25and N20, and v-SEP over the SI region was compared by measuring the distance from the sylvian fissure in each patient. Specifically, we drew a line that approximated the linear part of the sylvian fissure in each patient (see Fig. 5) and then measured the distance, at right angles, from this line to the maximum of each peak. This measure is a reasonable, first approximation of distance between the LEP and SEP distributions in the medial to lateral direction, which is the issue at hand.

**R**esults

Laser pulses with the intensity used in the present study evoked painful, pin–prick sensations in all 4 patients. The pain rating of the laser stimulus was 2.7/10 on average for Patient 1, 5/10 for Patient 2, 3–4/10 for Patient 3, and 4/10 for Patient 4. Patients were unsedated and alert during recording, as verified by the observation of the investigator applying stimuli to the patients hand (NW), by the patient’s accuracy in counting the total number of pulses, and by the patient’s ability to rate laser pulse stimuli approximately 6 times/min.

Typical LEP and SEP potentials from each of the 3 cortical areas are shown in Fig. 1 for Patient 2. The LEP N2* peaks were recorded over SI, parasylvian, and MF regions at peak latencies of approximately 140 ms. In contrast, vSEP was recorded first over SI with MF and parasylvian vSEP peaks recorded later. In the SI region, the N2* peak was distributed over both pre- and post-CS areas (Fig. 2), with the maximum just anterior to the CSe (electrode 1 in Fig. 1, A and B). The P2** peak revealed a similar distribution, but was associated with polarity reversal over the CSe (electrode 2, Fig. 1, A and B). As for the parasylvian region, the N2* peak was recorded with polarity reversal across the sylvian fissure (electrodes 3 and 4, Fig. 1, A and B), suggesting an opercular generator. P2** in the parasylvian region had 2 distinct distributions, one anteriorly and the other posteriorly along the sylvian fissure. Both of these potentials reversed polarity, the latter of which was not obviously related to any sulcus (Fig. 2, LEP P2**).

Over the MF region, both N2* and P2** peaks were recorded along the cingulate sulcus with polarity reversal over the most posterior part of the anterior cingulate gyrus just in front of the paracentral lobule (Figs. 1B and 2B).

The v-SEP peaks from upper extremity stimulation were recorded from SI (at 45 ms), parasylvian (95 ms), and MF (48 ms) regions (Figs. 1C and 2A). The v-SEP peak over the SI region showed polarity reversal across the CS (Figs. 1C and 2A). The distribution of this peak overlapped with e-SEP N20 maximum and with the finger motor area, as defined by cortical stimulation (Fig. 2A), but was located ventral to that of the 2 LEP peaks with minimal overlap (Fig. 2A). In the parasylvian region, the v-SEP peak showed polarity reversal across the SF, similar to LEP N2* peak (Figs. 1C and 2A). The distribution of v-SEPs in the MF region was similar to that of LEP peaks, but without polarity reversal. The e-SEP P25 component at 22 ms was recorded from a small post-CS area (Figs. 1D and 2A). The distribution of P25 was located between v-SEP and LEP peaks.

**LEP N2* and P2** peaks over the SI region

The LEP N2* peak was recorded in all 4 patients at an average latency of 148 ± 8 ms (mean ± SE) at the maxima (Figs. 1, 2, and 3) (Table 1). It was distributed over both pre-CSe (6.3 electrodes in average) and post-CSe (3.3 electrodes in average) areas. The maximum of N2* was always located over the CS or slightly anterior to it. No polarity reversal was found for N2* (Table 2). The P2** peak was also recorded from the SI region in all 4 patients with an average latency of 222 ± 19 ms at the maxima (Figs. 1, 2, and 4). Although its distribution was similar to that of N2*, the location of the P2** maximum was different from that of the N2* in 2 patients (Patients 3 and 4, Figs. 3 and 4). Polarity reversal was found for P2** in one patient (Patient 2).

The v-SEP at approximately 45 ms (Table 3) showed polarity reversal across CS with negativity over the precentral area (Figs. 2 and 3). Its maximum was always located posterior to CSe (Fig. 5). The e-SEP N20 maximum was within the distribution of the v-SEP peak (Figs. 2 and 3). The distribution of the e-SEP P25 peak was very small (Figs. 2 and 3), as typical for a near-field potential (0.5 electrodes in average over pre-CSe area, 3.5 post-CSe area), and the maximum P25 was always located on or posterior to CSe (Fig. 5). The area where cortical stimulation evoked hand/finger motor responses overlapped with that of the v-SEP peak (Figs. 2 and 3).

The N2* peak was distributed medial (dorsal) to e-SEP N20 maximum, P25, and v-SEP peak with minimal overlap (Figs. 2A, 3, and 5). The maximum of the N2* peak was located approximately 1–2 cm (1–2 interelectrode distances) medial to the e-SEP P25 maximum and 2–3 cm medial to the v-SEP maximum (Fig. 5). The distribution of the N2* peak (9.5 electrodes in average) was approximately 2.5 times as large as that of e-SEP P25 (4.0 electrodes, Figs. 2A and 3), suggesting a longer distance of its generators from the cortical surface. Because of their large size, the distributions of LEP N2* and P2** included the hand representation area in primary somatomotor cortex, although their peak location was clearly shifted medially from that representation. The locations of the maximum of LEP, e-SEP, and v-SEP were compared by measuring the distances from the linear part of the sylvian fissure (Fig. 5). The distance of LEP N2* (P = 0.03, 5.3 ± 0.5 cm, mean ± SE) and P2** (P = 0.03, 5.3 ± 0.2 cm) peak from the sylvian fissure was significantly longer than that of e-SEP N20 (3.3 ± 0.4) (Mann–Whitney test). Other comparisons were not made because of limited sample size.

**LEP N2* and P2** peaks over parasylvian and MF regions

Parasylvian and MF regions were covered by grids in 3 patients (Patients 2–4). In those patients, the N2* peak was...
recorded over the anterior part of the parasyvian region in 2 patients (Patients 2 and 3, Figs. 2A and 3B) and over the MF region in all 3 patients (Patients 2–4) (Figs. 1, 2B, and 6). The absence of a clear parasyvian N2* in Patient 4 may be attributable to insufficient coverage of the region inferior to the sylvian fissure (compare Fig. 2A and Fig. 3C). For the N2* peak, polarity reversal was found in 2 patients (Patients 2 and 3) for the parasyvian region anteriorly (Figs. 2A and 3B), and
in 2 patients (Patients 2 and 3) for the MF region (Figs. 2B and 6A, Table 2). The P2** peak was recorded from both regions in all 3 patients. In 2 patients who showed a N2* in the parastriate region (Patients 2 and 3, Figs. 2A and 4), the distribution of P2** was similar to that of N2* but with opposite polarity pattern. Patient 2 showed an additional peak at the posterior part of parastriate region (Fig. 2A). Patient 4 also revealed P2** polarity reversal dorsal to the sylvian fissure (Fig. 4).

The N2* peak recorded from the MF region showed polarity reversal, with positivity rostral, possibly along the cingulate sulcus, in 2 patients (Patients 2 and 3, Figs. 2B and 6A). P2** was distributed in a similar area with opposite polarity pattern, with negativity rostral, as compared with N2* in all 3 patients (Figs. 2B and 6). In Patient 4, the N2* and P2** peaks were recorded mainly over the supplementary motor area with polarity reversal of P2** near the precentral sulcus (Fig. 6B).

The v-SEP was recorded from the parastriate region at approximately 95 ms in 3 patients (Figs. 1, 2, and 3; latencies as labeled) and from the MF region at approximately
FIG. 3. Comparison of LEP N2*, e-SEP P25, and v-SEP peaks in Patients 1, 3, 4 (A–C). Convention as in Fig. 2, except that the polarity of the peak was expressed by black (negativity) and white (positivity) circles. Note clear difference in location in the SI region LEP N2* peaks medial to other potentials (e-SEP P25 and v-SEP). In contrast the LEP N2* has a similar distribution to the v-SEP distribution over parasylvian cortex in Patient 3 (B).

TABLE 1. LEP peak latency and amplitude of the maxima in SI, parasylvian, and MF regions

<table>
<thead>
<tr>
<th></th>
<th>N2* Maxima</th>
<th>P2** Maxima</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SI</td>
<td>Parasyvian</td>
</tr>
<tr>
<td></td>
<td>SI</td>
<td>Parasyvian</td>
</tr>
<tr>
<td>n</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>148 ± 8</td>
<td>159 ± 12</td>
</tr>
<tr>
<td>Amplitude (μV)</td>
<td>−93 ± 32</td>
<td>−54/−71</td>
</tr>
</tbody>
</table>

Values are means ± SE, n, number of patients available. * Absolute amplitude because of inconsistent polarity at the maximum.
TABLE 2. Polarity of LEP N2* and P2** peaks in SI, parasylvian, and MF regions

<table>
<thead>
<tr>
<th>Patient</th>
<th>SI N2*</th>
<th>SI P2**</th>
<th>Parasylvian N2*</th>
<th>Parasylvian P2**</th>
<th>MF N2*</th>
<th>MF P2**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N</td>
<td>PR</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>N</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>N</td>
<td>P</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>4</td>
<td>N</td>
<td>P</td>
<td>—</td>
<td>PR</td>
<td>N</td>
<td>PR</td>
</tr>
</tbody>
</table>

N, negative; P, positive; PR, polarity reversal —, no data available.

50 ms in 2 patients (Patients 2 and 4, Figs. 2B and 6B) (Table 3). The distribution of the v-SEP over the parasylvian region was similar to that of the LEP N2* (Patients 2 and 3, Fig. 2A) or the P2** peak (Patient 4, Fig. 3C), including the location of polarity reversal. The distribution of v-SEP in the MF region also overlapped with LEP peaks, but was not associated with polarity reversal.

FIG. 4. Amplitude distribution of LEP P2** peak over the convexity in Patients 1, 3 and 4. See also results from Patient 2 (Figs. 1 and 2). Conventions as in Fig. 3. For SI region, P2** was located predominantly over the pre-CSe area. Over the parasylvian region, a polarity reversal was observed near the sylvian fissure (Patients 3 and 4).

TABLE 3. Peak latency and amplitude of v-SEP and e-SEP P25 for SI, parasylvian, and MF regions

<table>
<thead>
<tr>
<th>Patient</th>
<th>v-SEP maxima</th>
<th>e-SEP P25</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Latency (ms)</td>
<td>Amplitude (µV)</td>
</tr>
<tr>
<td>SI</td>
<td>Parasylvian</td>
<td>MF</td>
</tr>
<tr>
<td>1</td>
<td>45 ± 5</td>
<td>93 ± 2</td>
</tr>
<tr>
<td>2</td>
<td>42 ± 10</td>
<td>29 ± 11*</td>
</tr>
</tbody>
</table>

Values are means ± SE, n, number of patients available. * Absolute amplitude because of inconsistent polarity at the maximum.

Amplitudes and latencies of LEPs over all three regions

Examination of the LEPs suggests that the N2* but not the P2** peaks were larger over SI than over the parasylvian region and MF (Tables 1 and 4). The differences in the mean N2* peak amplitude at all sites with significant N2* peaks were significantly different (one-way ANOVA, F = 3.9, P = 0.028) between SI, parasylvian region, and MF (Table 4). Post hoc testing (Tukey’s HSD test) revealed that the SI N2* tended to be greater than that recorded over the MF region (P = 0.056). Differences between the 3 cortical areas were also significant for the LEP P2** (one-way ANOVA, F = 3.2, P = 0.044). Post hoc testing (Tukey’s HSD) showed that the P2** amplitude in the parasylvian region tended to be larger than that recorded over SI (P = 0.073) and MF (P = 0.067) regions.

Mean latency of the N2* and P2** peaks at the maxima in the 3 regions is shown in Table 1. Overall, the peak latency of N2* was approximately 140–160 ms for all 3 regions, with the parasylvian region exhibiting the shortest latencies. The N2* peak of the maximum in the MF region was delayed by 10–15 ms in 2 patients (Patients 3 and 4) and almost the same as in SI in Patient 2. P2** peak latency was 220–240 ms. When compared for all sites where significant N2* and/or the P2** peaks were recorded (Table 4), the N2* latency in the 3 regions was not significantly different (one-way ANOVA, F = 0.6, P = 0.57). The difference in the P2** latency between the 3 regions was significant (F = 3.4, P = 0.036). Post hoc testing revealed that the P2** latency recorded over the parasylvian region was significantly longer than that over the SI region (Tukey’s HSD, P = 0.035), but not than that over the MF region.

DISCUSSION

This report demonstrates that discrete LEP N2* and P2** peaks can be recorded simultaneously from the cortical surface of 3 anatomically discrete regions (i.e., SI, parasylvian, and MF regions). The peak signals recorded in these 3 regions were separated by areas with absent or minimal LEP signals. Thus present data support the view (Lenz et al. 1998a,b) that LEPs recorded over cingulate and parasylvian cortex were not the result of far-field potentials but of local generators in the cingulate gyrus (Kitamura et al. 1995; Tarkka and Treede 1993; Valeriani et al. 1996; Vogel et al. 2003) and the parietal operculum (Kitamura et al. 1995; Tarkka and Treede 1993; Vogel et al. 2003). The present results extend those models by demonstrating that painful cutaneous laser stimuli consistently evoke large potentials recorded directly over the cortical surface of SI, at latencies consistent with input arising from nociceptors.
The LEP peaks recorded over the SI region were widely distributed over both pre- and postcentral areas, including the hand representation in the primary somatosensory and motor cortex. The LEP peak location was clearly medial (dorsal) to e-SEP and v-SEP peaks, consistent with previous MEG and EEG studies (Kanda et al. 2000; Ploner et al. 1999, 2000, 2002; Schlereth et al. 2003). The possibility that the present LEPs recorded from SI arise from a generator in the MF region is unlikely because: the LEP amplitudes are larger over SI than over the MF region (N2* peak), there is a polarity reversal over MF, and the latency is different between the SI and MF regions. Therefore these results provide strong, new evidence for the importance of SI in pain processing.

Methodological considerations

The latencies of LEP/LEP peaks in the literature are shown in Table 5 including scalp EEG, MEG, depth recording, and...
subdural recording with both CO₂ and Thulium YAG laser stimuli. Overall these earlier studies indicate that the N1 peak is recorded at 140–160 ms at temporal scalp leads, followed by N2 at 200–300 ms and P2 at 270–400 ms over the scalp vertex. It is interesting that the published results most consistently with the present results are also intracranial studies, specifically recordings carried out (CO₂ laser) through depth electrodes in the parietal operculum. These studies reported peak latencies at 140–170 ms (negativity–positivity) in the parietal operculum and in the deep insular area at 180–230 ms (negativity–positivity) (Frot and Mauguière 2003). Overall, this table documents differences in the latencies of the LEP components between the present results and those reported in previous literature.

We have labeled the first negative peak in the present results as N2* because it has always been followed by a positive peak (P2**). Although our N2* latency was similar to N1 latencies in the literature, N1 should have been followed by another negativity. A second negative peak or inflection on the first negative peak or a second positive peak (P3) was not apparent in these results on either side of the phase reversal (see Figs. 1 and 7). Therefore it is likely that the N2* and P2** peaks in the present results correspond to scalp the LEP N2 and P2 components reported in the previous literature.

### Table 4. LEP peak latency and absolute amplitude for SI, parasylvian, and MF regions

<table>
<thead>
<tr>
<th>Laser</th>
<th>Reference</th>
<th>N1 (Latency ms)</th>
<th>N2 (Latency ms)</th>
<th>P2 (Latency ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂</td>
<td>Scalp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bromm and Treede 1991</td>
<td>176 ± 18</td>
<td>233 ± 21</td>
<td>339 ± 28</td>
</tr>
<tr>
<td></td>
<td>Kakigi et al. 1991b</td>
<td>148</td>
<td>213</td>
<td>329</td>
</tr>
<tr>
<td></td>
<td>Beydoun et al. 1993</td>
<td>166 ± 12</td>
<td>249 ± 19</td>
<td>391 ± 28</td>
</tr>
<tr>
<td></td>
<td>Miyazaki et al. 1994</td>
<td>160</td>
<td>240</td>
<td>391 ± 28</td>
</tr>
<tr>
<td></td>
<td>Treede et al. 1988</td>
<td>160</td>
<td>240</td>
<td>391 ± 28</td>
</tr>
<tr>
<td></td>
<td>Tarkka and Treede 1993</td>
<td>160 ± 15</td>
<td>N2a 189 ± 15</td>
<td>290 ± 34</td>
</tr>
<tr>
<td></td>
<td>Valeriani et al. 1996</td>
<td>217 ± 40, SII 212 ± 12</td>
<td>242 ± 3</td>
<td>354–398</td>
</tr>
<tr>
<td>MEG</td>
<td>Kanda et al. 2000</td>
<td>SI 217 ± 40, SII 212 ± 12</td>
<td>242 ± 3</td>
<td>354–398</td>
</tr>
<tr>
<td></td>
<td>Kakigi et al. 1995</td>
<td>SII 220</td>
<td>242 ± 3</td>
<td>354–398</td>
</tr>
<tr>
<td></td>
<td>Frot et al. 2001</td>
<td>operculum 138 ± 15 (N140), 172 ± 13 (P170)</td>
<td>242 ± 3</td>
<td>354–398</td>
</tr>
<tr>
<td></td>
<td>Frot and Mauguière 2003</td>
<td>SII 220</td>
<td>242 ± 3</td>
<td>354–398</td>
</tr>
<tr>
<td>Subdural</td>
<td>Lenz et al. 1998a</td>
<td>operculum 137 ± 13 (N140), 172 ± 11 (P170)</td>
<td>242 ± 3</td>
<td>354–398</td>
</tr>
<tr>
<td></td>
<td>Lenz et al. 1998b</td>
<td>insula 180 ± 17 (N180), 226 ± 16 (P230)</td>
<td>242 ± 3</td>
<td>354–398</td>
</tr>
<tr>
<td>Thulium YAG</td>
<td>Scalp</td>
<td>145 ± 4</td>
<td>273 ± 10</td>
<td>325–352</td>
</tr>
<tr>
<td></td>
<td>Spiegel et al. 1996</td>
<td>SI 181 ± 7, operculum 158 ± 6, 3</td>
<td>273 ± 10</td>
<td>325–352</td>
</tr>
<tr>
<td></td>
<td>Spiegel et al. 2000</td>
<td>Si 174 ± 3, SII 163 ± 4</td>
<td>273 ± 10</td>
<td>325–352</td>
</tr>
<tr>
<td></td>
<td>Devos et al. 2000</td>
<td>SI 154 ± 8, SII 161 ± 6, ACC 188 ± 20</td>
<td>273 ± 10</td>
<td>325–352</td>
</tr>
<tr>
<td></td>
<td>Schlater et al. 2003</td>
<td>145 ± 4</td>
<td>325–352</td>
<td>325–352</td>
</tr>
</tbody>
</table>

Values are means ± SE, n, number of electrodes showing significant peak with amplitude >25% of the maximum in each region.

In addition to conventional e-SEP, we used vibratory stimulation (120 Hz), which could specifically activate Pacinian corpuscles (Johnson et al. 2000; Mountcastle 1984). The evoked responses to vibratory stimuli recorded from the SI region most likely represent the activity in area 3b (Ha-malainen et al. 1990; Hashimoto et al. 1998, 1999; Johnson et al. 2000). Although the e-SEP N20-P20 component is also shown to be generated in area 3b (Allison et al. 1989; Wood et al. 1985), we used v-SEP as a landmark of area 3b activation rather than e-SEP because of possible coactivation of tactile Aβ and nociceptive Aδ fibers by electrical stimulation of the median nerve (Treede et al. 1998). The P25 component of e-SEP was still used to localize the response in Brodmann’s area 1 (Allison et al. 1989; Wood et al. 1985) because in patients with epilepsy are similar to those in individuals without epilepsy.

All patients suffered from epilepsy with focal onset by criteria of history and imaging, and by the results of scalp and grid EEG recordings. Temporal lobe epilepsy is not associated with abnormalities on the neurologic (Adams et al. 1996) or sensory examination (Lenz et al. 1993, 1998a). Therefore there is reason to assume that the present results in patients with epilepsy are similar to those in individuals without epilepsy.

### Table 5. LEP latencies in the previous literature

<table>
<thead>
<tr>
<th>Laser</th>
<th>Reference</th>
<th>N1 (Latency ms)</th>
<th>N2 (Latency ms)</th>
<th>P2 (Latency ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂</td>
<td>Scalp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bromm and Treede 1991</td>
<td>249 ± 19</td>
<td>391 ± 28</td>
<td>336–341</td>
</tr>
<tr>
<td></td>
<td>Kakigi et al. 1991b</td>
<td>233 ± 21</td>
<td>369 ± 27</td>
<td>336–341</td>
</tr>
<tr>
<td></td>
<td>Beydoun et al. 1993</td>
<td>233 ± 21</td>
<td>369 ± 27</td>
<td>336–341</td>
</tr>
<tr>
<td></td>
<td>Miyazaki et al. 1994</td>
<td>233 ± 21</td>
<td>369 ± 27</td>
<td>336–341</td>
</tr>
<tr>
<td></td>
<td>Treede et al. 1988</td>
<td>233 ± 21</td>
<td>369 ± 27</td>
<td>336–341</td>
</tr>
<tr>
<td></td>
<td>Tarkka and Treede 1993</td>
<td>233 ± 21</td>
<td>369 ± 27</td>
<td>336–341</td>
</tr>
<tr>
<td></td>
<td>Valeriani et al. 1996</td>
<td>233 ± 21</td>
<td>369 ± 27</td>
<td>336–341</td>
</tr>
<tr>
<td></td>
<td>Kakigi et al. 1995</td>
<td>SII 220</td>
<td>354–398</td>
<td>354–398</td>
</tr>
<tr>
<td></td>
<td>Frot and Mauguière 2003</td>
<td>SII 220</td>
<td>354–398</td>
<td>354–398</td>
</tr>
<tr>
<td>Subdural</td>
<td>Lenz et al. 1998a</td>
<td>operculum 137 ± 13 (N140), 172 ± 11 (P170)</td>
<td>354–398</td>
<td>354–398</td>
</tr>
<tr>
<td></td>
<td>Lenz et al. 1998b</td>
<td>insula 180 ± 17 (N180), 226 ± 16 (P230)</td>
<td>354–398</td>
<td>354–398</td>
</tr>
<tr>
<td>Thulium YAG</td>
<td>Scalp</td>
<td>156 ± 23</td>
<td>211 ± 17</td>
<td>332 ± 34</td>
</tr>
<tr>
<td></td>
<td>Spiegel et al. 1996</td>
<td>156 ± 23</td>
<td>211 ± 17</td>
<td>332 ± 34</td>
</tr>
<tr>
<td></td>
<td>Spiegel et al. 2000</td>
<td>152 ± 20</td>
<td>208 ± 18</td>
<td>329 ± 34</td>
</tr>
<tr>
<td></td>
<td>Devos et al. 2000</td>
<td>152 ± 20</td>
<td>208 ± 18</td>
<td>329 ± 34</td>
</tr>
<tr>
<td></td>
<td>Schlater et al. 2003</td>
<td>145 ± 4</td>
<td>273 ± 10</td>
<td>325–352</td>
</tr>
<tr>
<td></td>
<td>Ploner et al. 1999</td>
<td>SI 181 ± 7, operculum 158 ± 6, 3</td>
<td>273 ± 10</td>
<td>325–352</td>
</tr>
<tr>
<td></td>
<td>Ploner et al. 2002</td>
<td>Si 174 ± 3, SII 163 ± 4</td>
<td>273 ± 10</td>
<td>325–352</td>
</tr>
</tbody>
</table>

J Neurophysiol • VOL 91 • JUNE 2004 • www.jn.org
LEPs in the SI region

LEP N2* and P2** peaks were directly and simultaneously recorded from SI, parasylvian, and medial frontal regions. These results are consistent with our previous subdural recordings from MF and parasylvian cortex separately (Lenz et al. 1998a,b). However, our own previous subdural recordings from parasylvian cortex did not reach far enough toward the midline to cover the region that we have now identified as the hand representation of SI (Lenz et al. 1998a). A case study of subdural recording has reported that significant LEPs can be recorded over SI (Kanda et al. 2000), consistent with the present results.

The distribution of LEP peaks was medial (dorsal) to that of v-SEP, e-SEP, and of finger/hand positive motor area, even close to midline (Fig. 5). This is also suggested by previous MEG and EEG studies (Kanda et al. 2000; Ploner et al. 1999, 2000, 2002; Schlereth et al. 2003). The proximity of the hand SI and MF cortical regions, might lead to the detection of a single generator between the 2 regions by source analysis, or to the identification of the SI LEPs as far-field potentials. However, there are several reasons to identify the LEP recorded over SI as a near-field potential arising from SI. First, the N2* LEP amplitude in the SI region in our patients tended to be larger than that recorded from the MF region ($P = 0.056$) (Tables 1 and 4). Second, the latencies of N2* and P2** peaks were different between SI and MF regions in each patient individually (cf. N2* in Patient 2, Fig. 2A). A recent MEG study differentiated between SI and the anterior cingulate cortex (ACC) sources by their different time course of activation (Ploner et al. 2002). Third, N2* and P2** peaks in MF region often showed polarity reversal (Table 2), which suggests a horizontal dipole in the cingulate sulcus. Fourth, SI and MF regions did not show the reversed polarity expected for a single source between 2 recording surfaces.

The SI N2* peak may indicate the arrival of input originating from nociceptors. Cutaneous laser stimulation evokes a pure pain sensation attributed to selective activation of nociceptors (Bromm and Treede 1984; Carmon et al. 1976, 1978; Lenz et al. 1998a,b). LEP latencies attributable to direct conduction from the hand would be predicted at approximately 170 ms based on 40-ms $\Delta T$ receptor activation time (Bromm and Treede 1984), 100-ms conduction delay in the peripheral nerve (A$\delta$ fibers, 8–12 m/s) (Beydoun et al. 1997; Kakigi et al. 1991a; Kenton et al. 1980), and 30-ms conduction delay through the STT (8–10 m/s) (Kakigi and Shibasaki 1991). Thus the first negative wave of the LEP may represent the cortical response evoked by the afferent volley resulting from activation of nociceptors by the laser stimulus.

The possible generator sources of LEP peaks recorded from the SI region

The distribution of e-SEP P25 and v-SEP peaks was consistent with the generator in area 1 (Allison et al. 1989; Wood et al. 1988) and area 3b (Hamalainen et al. 1990; Hashimoto et al. 1998, 1999; Jones and Friedman 1982; Jones et al. 1982), respectively. Recent EEG/MEG (Kanda et al. 2000; Ploner et al. 2000; Schlereth et al. 2003) and imaging (Gelnar et al. 1999) studies suggested that Brodmann’s area 1 in SI cortex receives nociceptive input, consistent with monkey studies (Chudler et al. 1990; Kenshalo Jr and Isensee 1983; Kenshalo Jr and Willis 1991). However, the LEP N2* peak was distributed more diffusely through the pre- and postcentral areas without polarity reversal, unlike the distributions of e-SEP N20, P25, and v-SEP peaks. These results could be explained by a generator deep on the posterior wall of the central sulcus (area 3a) or in and posterior to the postcentral sulcus (areas 2, 5, or 7) (Craig 1995; Tommerdahl et al. 1996; cf. Valeriani et al. 2003).

Both MEG and EEG source analysis data have suggested a tangentially oriented current source in the SI region (Ploner et al. 1999; Ploner et al. 2000; Schlereth et al. 2003). Imaging studies (Gelnar et al. 1999) suggested that Brodmann’s area 1 in SI cortex receives nociceptive input, consistent with monkey studies (Chudler et al. 1990; Kenshalo Jr and Isensee 1983; Kenshalo Jr and Willis 1991). However, the LEP N2* peak was distributed more diffusely through the pre- and postcentral areas without polarity reversal, unlike the distributions of e-SEP N20, P25, and v-SEP peaks. These results could be explained by a generator deep on the posterior wall of the central sulcus (area 3a) or in and posterior to the postcentral sulcus (areas 2, 5, or 7) (Craig 1995; Tommerdahl et al. 1996; cf. Valeriani et al. 2003).
al. 1999, 2000, 2002; Schlereth et al. 2003), of which our grid recordings may only have covered the negative pole. The positive pole of the dipole generating the present LEPs could have been located further posterior if the generator were located in areas 2, 5, or 7 (Schlereth et al. 2003). Alternatively, the positive pole could have been located anteriorly if there were 2 independent sources in the primary motor cortex and Brodmann’s area 1 and/or area 2 (Gel nar et al. 1999; Kanda et al. 2000).

**LEP in parasyylvian and MF regions**

Over the MF region, the N2* and P2** peaks were distributed in a similar area with an opposite pattern of polarity reversal near the cingulate sulcus (Figs. 2B and 6). This suggests that N2* and P2** are generated by a horizontal current source in the sulcus, possibly the cingulate gyrus. One patient (Patient 4) showed a more dorsal distribution, possibly on the supplementary motor area. The N2* latency in the MF region was almost identical to that in SI and parasyylvian regions in Patient 2 and delayed by 10–15 ms in Patients 3 and 4. This might be consistent with scalp EEG studies (Valeriani et al. 1996, 2000) and an MEG study (Ploner et al. 2002) where the (equivalent) current source corresponding to the N2* peak in ACC is shown to be delayed by 20–30 ms from that in parasyylvian region. The location of polarity reversal was near the anterior border of the paracentral lobule, consistent with the results of source analysis studies on scalp LEPs (Bentley et al. 2001, 2002, 2003; Bromm and Lorenz 1998; Schlereth et al. 2003) and those of imaging studies (Casey et al. 1996; Coghill et al. 1999; Gel nar et al. 1999; Kwan et al. 2000; Porro et al. 1998; Tolle et al. 1999; Vogt et al. 1996).

In conclusion, we have demonstrated that the N2* and P2** peaks can be recorded directly over the postcentral gyrus, suggesting that SI cortex is the generator of the LEPs recorded from the high central convexity of the hemisphere. Numerous imaging and electrophysiological studies have either endorsed or minimized the role of SI in pain perception. Neuronal recordings in monkeys (Kenshalo Jr and Issensee 1983; Kenshalo Jr and Willis 1991) and some imaging studies in humans (Bushnell et al. 1999; Hofbauer et al. 2001) have supported the role of SI in pain. In the SI region, the distribution of N2* and P2** peaks was different from that of vibratory SEP and electrically evoked SEP P25. This distribution pattern suggests that the generator sources of the LEP N2* peak are situated outside of Brodmann’s area 1 on the crest of the postcentral gyrus, or area 3b on the posterior bank of the central sulcus (Brodmann 1909; Naidich 1991), perhaps in area 3a, deep in the central sulcus. Source analysis of subdural LEPs recorded directly from the pre- and postcentral gyri may have the resolution to settle the issue (Vogel et al. 2003).

**Acknowledgments**

We thank D. Jackson and L. H. Rowland for excellent technical assistance.

**References**


Brodmann K. *Vergleichende Lokalisationslehre der Grosshirnrinde.* Germany: J. A. Barth, 1907.


