Cutaneous painful laser stimuli evoke responses recorded directly from primary somatosensory cortex in awake humans

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Abbreviated title: Subdural N2 laser evoked potentials are maximal over human SI.

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Abstract

Negative and positive laser evoked potential (LEP) peaks (N2*, P2**) were simultaneously recorded from the primary somatosensory (SI), parasyylvian, and medial frontal (MF – anterior cingulate and supplementary motor area) cortical surfaces 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, parasyylvian 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 parasyylvian 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 parasyylvian region. The amplitude of N2* was larger over SI than over MF and the latencies of the LEP peaks in those two regions were different. These findings provide evidence for a significant LEP generator in the post-central gyrus, perhaps SI cortex, that is situated outside the tactile homunculus in SI and that receives its input arising from nociceptors simultaneously with parasyylvian and MF cortex.

Keywords: laser evoked potential, human, primary and secondary somatosensory cortex, vibrotactile, subdural recording
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; Derbyshire et al. 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 which modulate the perceived intensity of the painful stimulus (Bushnell et al. 1999; Hofbauer et al. 2001) and in those which employ 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 magneto-encephalographic (MEG - laser evoked field, LEF) studies have failed to detect an SI generator (Bromm et al. 1996; Bromm and Chen 1995; Huttunen et al. 1986; Kakigi et al. 1995; Valeriani et al. 1996; Valeriani et al. 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 LEF and LEP source analysis studies have identified a generator in the SI region (Kanda et al. 2000; Ploner et al. 1999; Ploner et al. 2000; Ploner et al. 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 parasympathetic 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, parasympathetic, 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 three 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.

**Abbreviations**

- CSe, the central sulcus defined by e-SEP N20-P20 polarity reversal
- LEF, laser evoked magnetic field
- LEP, laser evoked potential composed of early N2* and later P2** responses in our studies which were earlier than the N2 and P2 potentials described previous studies (Table 5). The asterisk has been added to the N2/P2 labels to acknowledge that difference.
- MF, medial frontal composed of the anterior cingulate and supplementary motor area
- SI, the primary somatosensory cortex
- SEP, the somatosensory evoked potential

  - e-SEP, SEP following electric stimulation of the medial nerve at wrist

  - v-SEP, SEP following vibrotactile stimulation on the middle finger tip

  - significant evoked potential peaks, peaks with the peak amplitude greater than the mean + 2 SD pre-stimulus level.

**Materials and 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 fronto-parietal area (Patient 1, Figures 3-6), right lateral convexity and medial fronto-parietal area (Patient 2, Figures 1, 2 and 5), and left lateral fronto-parietal convexity and medial fronto-parietal area (Patient 3 and 4, Figures 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 peri-vascular spaces (Adams et al. 1996) (Patient 2) and a small cavernoma in the right parietal lobe (contralateral 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 those 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 2µm, duration 1 ms - Wavelight Inc., Starnberg, Germany). A laser beam of approximately 6 mm diameter was applied to the dorsum of the hand contralateral to the side 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 sensation 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 inter-stimulus interval (ISI) of 7-11 s. Sessions were repeated with interval of 1-2 minutes. In the present study, we only analyzed evoked responses 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 Patient 3 and 4) were delivered randomly with ISI of 5-10 s. Two sessions were recorded with the interval of 1-2 minutes. Patient 1 was asked to rate pain intensity after each laser pulse. Patient 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; Beydoun et al. 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 interstimulus interval 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 Patient 2-4 (Figures 1, 2, 3B and 3C). 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 grams. 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 sec. At least two runs were obtained.

**Data acquisition**

Cortical electrical activities were recorded from subdural grid electrodes (electrocorticogram, ECoG). The electrodes consisted of platinum-iridium circular electrodes (2.3mm 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 up to 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, Inc., West Warwick, RI). All ECoG signals 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 1000 to 2500 Hz and recorded to computer hard disk along with stimulus markers for subsequent offline analysis.

**Anatomical Correlation of Cortical Functions**

Sensory, motor and language function was mapped by means of cortical stimulation and recording of e-SEPs, as described elsewhere (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 to 5 s duration. This technique produced excitation beneath both of the stimulated electrodes in a pair (Ranck, 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, intra-operative observation and photographs, and peri-operative radiological studies including superimposition (3D CT-MRI) of three-dimensional post-operative computed tomography (CT) on three-dimensional pre-operative MRI data sets, as in previous studies (Boatman et al. 1997; Crone et al. 1998; Lenz et al. 1998a; Lenz et al. 1998b). e-SEP N20-P20 polarity reversal (CSe) and intra-operative pictures were consistent in terms of CS location in 3 patients who had intra-operative pictures available (Patient 2-4). SF location based on intra-operative picture was consistent with 3D CT-MRI data in Patient 4. In Patients 2 and 3, SF was not clearly visible in intra-operative 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 was 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) were also shown in each figure.

The positions of subdural electrodes on the interhemispheric surface were determined by superimposition of mid-sagittal plane of the pre-operative T1 weighted MRI and the lateral view of skull X-ray taken after implantation of grids for Patient 2 and 3 (Ikeda et al. 1995; Ikeda et al. 1996; Ohara et al. 2000b; Ohara et al. 2000a; Ohara et al. 2001). For Patient 4, we used mid-sagittal plane of post-operative 3D CT instead of lateral view of skull X-ray.

Data analysis

Multi-channel ECoG signals were re-montaged using an average reference to minimize the influence of location and activity of the reference electrode (Crone et al. 1998; Lehmann 1987). ECoG 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 pre-stimulus period was used for LEPs and v-SEPs and a time window of 120 ms with 20 ms pre-stimulus period for e-SEPs. Responses to individual laser pulse and vibratory stimulus 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 two recording sessions. A total of 30-76 responses for LEP,
142-220 for v-SEP and 2018-5200 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 pre-stimulus 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 pre-stimulus 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; Kitamura 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 diameter as a function of amplitude (Figures 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 1 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 P25 and 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 which approximated the linear part of the sylvian fissure in each patient (see Figure 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.

Results

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 in 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 patient’s 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 six times per minute.

Typical LEP and SEP potentials from each of the three cortical areas are shown in Figure 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 (Figure 2), with the maximum just anterior to the CSe (electrode 1 in Figures 1A and 1B). The P2** peak revealed a similar distribution, but was associated with polarity reversal over the CSe (electrode 2, Figures 1A and 1B). As for the parasylvian region, the N2* peak was recorded with polarity reversal across the sylvian fissure (electrodes 3 and 4, Figures 1A and 1B), suggesting an opercular generator. P2** in the parasylvian region had two 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 (Figure 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 (Figures 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 (Figures 1C and 2A). The v-SEP peak over the SI region showed polarity reversal across the CS (Figures 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 (Figure 2A) but was located ventral to that of the two LEP peaks with minimal overlap (Figure 2A). In the parasylvian region, the v-SEP peak showed polarity reversal across the SF, similar to LEP N2* peak (Figures 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 (Figures 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 $148 \pm 8$ ms (mean $\pm$ SE) at the maxima (Figures 1, 2 and 3) (Table 1). It was distributed over both pre-CS (6.3 electrodes in average) and post-CS (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*
The P2** peak was also recorded from the SI region in all 4 patients with an average latency of $222 \pm 19$ ms at the maxima (Figures 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 (Patient 3 and 4, Figures 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 pre-central area (Figures 2 and 3). Its maximum was always located posterior to CSe (Figure 5). The e-SEP N20 maximum was within the distribution of the v-SEP peak (Figures 2 and 3). The distribution of the e-SEP P25 peak was very small (Figures 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 (Figure 5). The area where cortical stimulation evoked hand/finger motor responses overlapped with that of the v-SEP peak (Figures 2 and 3).

The N2* peak was distributed medial (dorsal) to e-SEP N20 maximum, P25 and v-SEP peak with minimal overlap (Figures 2A, 3 and 5). The maximum of the N2* peak was located approximately 1-2 cm (1-2 inter-electrode distances) medial to the e-SEP P25 maximum and 2-3 cm medial to the v-SEP maximum (Figure 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, Figures 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 sensorimotor 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 (Figure 5). The distance of LEP N2* ($p=0.03$, $5.3\pm0.5$ cm, mean±SE) and P2** ($p=0.03$, $5.3\pm0.2$ cm) peak from the sylvian fissure was significantly longer than that of e-SEP N20 ($3.3\pm0.4$) (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 (Patient 2-4). In those patients, the N2* peak was recorded over the anterior part of the parasylvian region in 2 patients (Patient 2 and 3, Figures 2A and 3B) and over the MF region in all 3 patients (Patients 2-4) (Figures 1, 2B and 6). The absence of a clear parasylvian N2* in Patient 4 may be due to insufficient coverage of the region inferior to the sylvian fissure (compare Figure 2A and 3C). For the N2* peak, polarity reversal was found in 2 patients (Patient 2 and 3) for the parasylvian region anteriorly (Figures 2A and 3B), and in 2 patients (Patient 2 and 3) for the MF region (Figures 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 parasympathetic region (Patients 2 and 3, Figures 2A and 4), the distribution of P2** was similar to that of N2* but with opposite polarity pattern. Patient 2 showed additional peak at the posterior part of parasympathetic region (Figure 2A). Patient 4 also revealed P2** polarity reversal dorsal to the sylvian fissure (Figure 4).

The N2* peak recorded from the MF region showed polarity reversal, with positivity rostral, possibly along the cingulate sulcus, in 2 patients (Patient 2 and 3, Figure 2B and 6A). P2** was distributed in a similar area with opposite polarity pattern, with negativity rostral, as compared to N2* in all 3 patients (Figures 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 pre-central sulcus (Figure 6B).

The v-SEP was recorded from the parasympathetic region at approximately 95 ms in 3 patients (Figures 1, 2, and 3B-C – latencies as labeled) and from the MF region at approximately 50 ms in 2 patients (Patient 2 and 4, Figures 2B and 6B) (Table 3). The distribution of the v-SEP over the parasympathetic region was similar to that of the LEP N2* (Patient 2 and 3, Figures 2A) or the P2** peak (Patient 4, Figure 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.

**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 (1 way ANOVA, \( F=3.9, p=0.028 \)) between SI, parasylvian region, and MF (Table 4). Post hoc testing (Tukey’s honestly significant difference (HSD) test) revealed that the SI N2* tended to be greater than that recorded over MF region \((p=0.056)\). Differences between the three cortical areas were also significant for the LEP P2** (1 way ANOVA, \( F=3.2, p=0.044 \)). Post hoc testing (Tukey’s HSD) showed that the P2** amplitude in 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 three 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 (Patient 3 and 4) and almost 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 three regions was not significantly different (1 way ANOVA, \( F=0.6, p=0.57 \)). The difference in the P2** latency between the three regions was significant \((F=3.4, p=0.036)\). Post hoc testing revealed that the P2** latency recorded
over the parasyylvian 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 three anatomically discrete regions, i.e. SI, parasyylvian 
and MF regions. The peak signals recorded in these three regions were separated by areas with 
absent or minimal LEP signals. Thus, present data supports the view (Lenz et al. 1998a; Lenz et al. 
1998b), that LEPs recorded over cingulate and parasyylvian 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 
post-central 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; Ploner et al. 2000; Ploner et al. 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 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/LEF 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 consistent 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 Mauguiere 2003). Overall, this table documents differences in the latencies of the LEP components between the present results and the 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 inflexion 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 Figures 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 in the previous literature.

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 (Hamalainen et al. 1990; Hashimoto et al. 1998; Hashimoto et al. 1999; Johnson et al. 2000). Although 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 no alternative method is available.
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 exam (Lenz et al. 1993; Lenz et al. 1998a). Therefore, there is reason to assume that the present results in patients with epilepsy similar to those in individuals without epilepsy.

**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; Lenz et al. 1998b). However, our own previous subdural recordings from parasylvian cortex did not reach far enough towards 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 (Figure 5). This is also suggested by previous MEG and EEG studies (Kanda et al. 2000; Ploner et al. 1999; Ploner et al. 2000; Ploner et al. 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 two 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 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, Figure 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 due to selective activation of nociceptors (Bromm and Treede 1984; Carmon et al. 1976; Carmon et al. 1978; Lenz et al. 1998a; Lenz et al. 1998b). LEP latencies attributable to direct conduction from the hand would be predicted at approximately 170 ms based on 40 ms $\alpha$ receptor activation time (Bromm and Treede 1984), 100 ms conduction delay in the peripheral nerve ($\alpha$ fibers – 8-12m/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
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; Hashimoto et al. 1999; Jones et al. 1982; Jones and Friedman 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 post-central 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 post-central 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; Ploner et al. 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 area 2, 5, or 7 (Schlereth et al. 2003). Alternatively, the positive pole could have been located anteriorly if there were two independent sources in the primary motor cortex and Brodmann’s area 1 and/or 2 (Gelnar et al. 1999; Kanda et al. 2000).

**LEP in parasyvian 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 (Figures 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 over the supplementary motor area. The N2* latency in the MF region was almost identical to that in SI and parasyvian regions in Patient 2 and delayed by 10-15 ms in Patient 3 and 4. This might be consistent with scalp EEG studies (Valeriani et al. 1996; Valeriani et al. 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 parasyvian 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; Bentley et al. 2002; Bentley et al. 2003; Bromm and Lorenz 1998; Schlereth et al. 2003) and those of imaging studies (Casey et al. 1996; Coghill et al. 1999; Gelnar et
Summary and conclusions

In conclusion, we have demonstrated that the N2* and P2** peaks can be recorded directly over the post-central 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 Isensee 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 post-central gyrus, or area 3b on the posterior bank of the central sulcus (Brodmann 1907; Naidich 1991), perhaps in area 3a, deep in the central sulcus. Source analysis of subdural LEPs recorded directly from the pre- and post-central gyri may have the resolution to settle the issue (Vogel et al. 2003).
Acknowledgement

This work is supported by the National Institutes of Health – National Institute of Neurological Disorders and Stroke (NS38493 and NS40059 to FAL) and Deutsche Forschungsgemeinschaft (Tr236/13-2 to RDT). We thank D. Jackson and L. H. Rowland for excellent technical assistance.
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Ref Type: In Press


Figure legends

Figure 1  LEP, e-SEP and v-SEP recorded from SI, parasylvian and MF regions in Patient 2

Representative waveforms of LEP in B, v-SEP in C, and e-SEP in D in Patient 2 are shown. Numbers at the left upper corner of each waveform correspond to the electrode location represented by the same numbers in maps of the brain - A. B - LEPs (N2* and P2** peaks) recorded at the sites as indicated in A. Electrodes are separated by 1cm along perpendicular lines within the grid. The peak latency of N2* and P2** peaks at 140 ms and 220 ms, approximately. Note the polarity reversal in SI region for P2** peak (top row), in parasylvian region for N2* peak (middle row) and in MF region for both N2* and P2** peaks (bottom row). Peaks interpreted as N2* and P2** are labeled by * and ** in the figure and text to indicate the corresponding peaks, on both polarities of the phase reversal. C. v-SEP was also recorded from all 3 regions. D - P25 component of e-SEP was recorded at the peak latency of 22 ms.

Figure 2  Amplitude distribution of LEP N2* and P2** peaks, v-SEP (peaks as labeled) and e-SEP P25 in Patient 2  Distribution of LEP, v-SEP (peak latency at 45 and 95 ms) and e-SEP (P25) peaks over the convexity (A) and the medial wall (B) of the hemisphere in Patient 2. Each circle or dot in the schematic brain represents electrode position. The amplitude of the peaks is
shown by diameter of the circle and the polarity is shown by the color of the circle (blue positivity, red negativity) as shown in the table at the lower right of A and B. Grey dots indicate absence of significant peaks. A heavy, black, dashed line represents e-SEP N20-P20 polarity reversal (CSe). The maximum of e-SEP N20 is indicated by an arrowhead. Large (> 1cm) gray ovals indicate electrode pairs where bipolar cortical stimulation evoked positive finger motor responses. Note that significant N2* and P2** peaks are distributed over SI, parasyvian, and MF regions. In SI region, N2* and P2** peaks was located medial to the v-SEP, e-SEP P25 and finger positive motor area. Clear polarity reversal was found in parasyvian and MF regions for both LEP N2* and P2**, with a distribution similar to v-SEP. Other conventions as for Figure 1.

Figure 3  Comparison of LEP N2*, e-SEP P25 and v-SEP peaks in Patient 2-4 (A-C)
Convention as in Figure 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 parasyvian cortex in Patient 3 (B).

Figure 4 Amplitude distribution of LEP P2** peak over the convexity in Patients 1, 3 and 4.
See also results from Patient 2 (Figures 1 and 2). Conventions as in Figure 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).

**Figure 5  The maximum of LEP, v-SEP and e-SEP peaks over SI region**  The maximum of LEP N2* and P2** is located 1-2 cm medial to e-SEP P25 maximum (E), approximately 2 cm medial to e-SEP N20 maximum (arrowhead), and 2-3 cm medial to v-SEP maximum (V). Conventions as in Figure 3. Thin dotted lines over the parasylvian region indicate lines which best approximate the linear part of the sylvian fissure. The distance of the maximum of each peak was measured perpendicular to these lines.

**Figure 6  Peak amplitude distribution of LEP N2*, P2** and v-SEP over the medial surface of brain in Patient 3 (A) and 4 (B)**  See also results from Patient 2 (Figures 1 and 2). Convention as in Figure 3. LEP N2* and P2** peak was recorded along the cingulate sulcus with clear polarity reversal (Patient 3, A; see also Patient 2 in Figures 1A, 1B, and 2B) and over the area including the supplementary motor area (Patient 4, B).
Figure 7  LEP waveforms over SI, parasylvian and MF regions in Patient 1, 3 and 4    Note

clear N2* and P2** peaks over each of three regions.  See also results from Patient 2 (Figure 1).
Table 1  LEP peak latency and amplitude of the maxima in SI, parasyylvian and MF regions

(\text{mean} \pm \text{SE})

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<th>P2** maxima</th>
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<td>amplitude (µV)</td>
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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

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N, negative; P, positive; PR, polarity reversal; -, no data available.
Table 3  Peak latency and amplitude of v-SEP and e-SEP P25 for SI, parasylvian and MF regions

(mean ± SE)

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<td>latency (ms)</td>
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<td>amplitude (µV)</td>
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n, number of patients available;* absolute amplitude because of inconsistent polarity at the maximum
Table 4   LEP peak latency and absolute amplitude for SI, parasyylvian and MF regions
(mean ± SE)

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n, number of electrodes showing significant peak with amplitude >25% of the maximum in each region
Table 5  LEP latencies in the previous literatures

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<td>233 ± 25</td>
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Figure 1
Figure 2
Figure 3
Figure 6
Figure 7