Dipole source analyses of laser evoked potentials obtained from subdural grid recordings from primary somatic sensory cortex

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Baumgärtner U, Vogel H, Ohara S, Treede RD, Lenz FA. Dipole source analyses of laser evoked potentials obtained from subdural grid recordings from primary somatic sensory cortex. J Neurophysiol 106: 722–730, 2011. First published May 18, 2011; doi:10.1152/jn.00135.2011.—The cortical potentials evoked by cutaneous application of a laser stimulus (laser evoked potentials, LEP) often include potentials in the primary somatic sensory cortex (S1), which may be located within the subdivisions of S1 including Brodmann areas 3A, 3B, 1, and 2. The precise location of the LEP generator may clarify the pattern of activation of human S1 by painful stimuli. We now test the hypothesis that the generators of the LEP are located in human Brodmann area 1 or 3A within S1. Local field potential (LFP) source analysis of the LEP was obtained from subdural grids over sensorimotor cortex in two patients undergoing epilepsy surgery. The relationship of LEP dipoles was compared with dipoles for somatic sensory potentials evoked by median nerve stimulation (SEP) and recorded in area 3B (see Baumgärtner U, Vogel H, Ohara S, Treede RD, Lenz FA. J Neurophysiol 104: 3029–3041, 2010). Both patients had an early radial dipole in S1. The LEP dipole was located medial, anterior, and deep to the SEP dipole, which suggests a nociceptive dipole in area 3A. One patient had a later tangential dipole with positivity posterior, which is opposite to the orientation of the SEP dipole in area 3B. The reversal of orientations between modalities is consistent with the cortical surface negative orientation resulting from superficial termination of thalamocortical neurons that receive inputs from the spinothalamic tract. Therefore, the present results suggest that the LEP may result in a radial dipole consistent with a generator in area 3A and a putative later tangential generator in area 3B.

NOCICEPTIVE STIMULI MAY PRODUCE increased blood flow (PET) and increased blood oxygen level-dependent (BOLD, MRI) signals in contralateral human primary somatic sensory cortex S1 (Apkarian et al. 2005; Bushnell et al. 1999; Lenz et al. 2010). Electroencephalographic and magnetoencephalographic (MEG) scalp recordings have been used to identify a laser evoked potential (LEP) dipole, which is medial and posterior of the somatosensory evoked potential (SEP) (N20–P20) generator (Ploner et al. 2000; Schlereth et al. 2003; Tarvainen and Treede, 1993; Timmermann et al. 2001). Human MEG studies have estimated the location of the nociceptive generator in S1 (Ploner et al. 1999b; Tommerdahl et al. 1998). However, some imaging studies have suggested that nociceptive stimuli often fail to activate S1 (Derbyshire and Jones 1998; Iadarola et al. 1998; Jones et al. 1991). This question has also been addressed by studies of S1 using single neuron activity and intrinsic optical signals in anesthetized monkeys (Kenshalo and Willis 1991; Tommerdahl et al. 1996; Whitel et al. 1999, 2009). These studies suggest that nociceptive heat stimuli may result in the activation of subdivisions of S1 including Brodmann area 3A in the depths of the central sulcus (Tommerdahl et al. 1996), area 1 at the crown of the postcentral gyrus, or the border zone between Brodmann areas 1 and 3B in the posterior wall of the central sulcus (Kenshalo and Isensee 1983). Finally, functional MRI (fMRI) studies in humans demonstrate activation of area 1 by nociceptive heat stimuli, which overlapped with activation by vibration and by a motor task (Gelnar et al. 1999; cf. Tommerdahl et al. 1996).

To improve the resolution of the estimated location of human S1 nociceptive cortex in humans, we have carried out source analysis of the response to nociceptive heat recorded by subdural electrodes. An important strategy to study human neuronal mechanisms of nociception is to use a cutaneous laser stimulus to activate nociceptors (Bromm and Treede 1984; Carmon et al. 1976, 1978) and to evoke the LEP from forebrain structures. Comparisons of scalp, subdural, and depth recordings have clarified early nociceptive signal processing in parieto-occipital cortex areas including S2 and posterior insula (Garcia-Larrea et al. 2003; Lenz et al. 2010).

However, the relationship of the LEP to pain sensations must be interpreted with caution, since their generators may also process nonnociceptive somatosensory inputs and may depend on the salience of the stimulus and on directed attention (Legrain et al. 2005, 2011; Lorenz and Garcia-Larrea 2003; Mouraux and Iannetti 2009; Siedenberg and Treede 1996; Zasiansky et al. 1996).

We now test the hypothesis that the generators of the LEP in S1 are located within human Brodmann area 1 or 3A (Ohara et al. 2004b). We have employed subdural recordings that apply unprecedented resolution and clarity to our approach to this hypothesis. The dipoles of the LEP were located relative to the generators of the SEP N20 in area 3B (Hamalainen et al. 1990; Hashimoto et al. 1998; Johnson 2001) and in area 1 (Allison et al. 1989; Baumgärtner et al. 2010).

METHODS

This study was carried out during the week between implantation and removal of grids of electrodes for presurgical investigation of...
intractable frontal lobe epilepsy. In a companion paper (Baumgärtner et al. 2010), we had reported recordings from subdural grids implanted for surgical treatment of medically intractable seizures. The recordings were analyzed for dipole source activations evoked by stimulation of tactile afferents in four patients (patients 1–4, 3 women and 1 man, 21–51 yr old); analysis revealed sources in Brodmann areas 3B and 1 (Baumgärtner et al. 2010). Although more than one grid was implanted in the subdural space in order to identify the seizure onset, the recordings described here were derived from one 8 × 8 (64 channel) grid that was located over the superior, frontotemporal convexity in all four cases. All grids were on the left except that in patient 2, which was on the right.

The present study focuses upon two of those patients (patients 1 and 2, both women, 21 and 51 yr old). Patients 3 and 4 of the original sample yielded LEP similar to those in Fig. 1 (see below). However, the dipole source analysis could not be performed in these patients (3 and 4) for technical reasons related to the signal-to-noise ratio and the lack of clear component structure of the global field power (GFP).

All patients were evaluated clinically by a neurologist with expertise in epilepsy and by a neurosurgeon, which included a standard bedside somatosensory testing protocol (Lenz et al. 1993). The study was approved by the Institutional Review Board of the Johns Hopkins University, and all patients gave informed consent.

**Experimental protocols.** During the entire recording session, continuous white noise was delivered to each ear through earphones (Click-tone module, Grass-Telefactor, West Warwick, RI). The subject reclined in bed with eyes open, quietly wakeful, while vision of the site of stimulation was occluded. SEP recordings were carried out with the same technique described in the companion paper (Baumgärtner et al. 2010).

SEP were recorded by electrically stimulating the median nerve at the wrist contralateral to the side of grid implantation with an interstimulus interval of 213 ms. The duration of the constant current square pulses was 300 μs, and the intensity was set at ~15–20% above the motor threshold. For the SEP, 2,018–5,200 responses were averaged time-locked to the stimulus with a time window of 120 ms and 20-μs prestimulus periods (see Baumgärtner et al. 2010).

During the laser studies, the patient wore protective glasses. Radiant heat stimuli were delivered to the hand dorsum contralateral to the implanted grid with a thulium YAG laser (wavelength 2 μm, duration 1 ms; StarMedToE, Starnberg, Germany). The laser beam of ~6–μm diameter was shifted slightly after each stimulus to avoid nociceptor fatigue and to prevent overheating of the skin.

To produce a comparable psychological state during the laser protocol, patients were instructed to count the stimuli (García-Larrea et al. 1997; Legrain et al. 2002; Siedenberg and Treede 1996). Laser pulses with a fixed energy level (720 mJ for patient 1, 560 mJ for patient 2) elicited pain graded at 3/10 to 4/10 on a visual analog scale, on which 10 is the most painful stimulus imaginable. These stimuli were delivered randomly with interstimulus intervals between 5 and 10 s.

For the LEP, the responses for 2 blocks of 40 stimuli for a total of 80 stimuli were included in the average with a time window of 1,500 ms and a 500-ms poststimulus interval. Responses to individual laser pulse stimulus were reviewed, and trials with artifacts or large baseline fluctuation were excluded before averaging, to a maximum of 15 trials, before recordings were repeated.

**Local field potential recordings.** Cortical electrical activities were recorded with grid electrodes (local field potentials [LFP]). 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). LFP from subdural grid electrodes were amplified and band-pass filtered at 0.1–300 Hz with Grass amplifiers (12A5, Astro-Med, West Warwick, RI).

All LFP signals were referenced to a single intracranial (subdural) reference electrode on a grid from the 8 × 8 grid over SI. These electrodes were located over prefrontal cortex (patient 1: lateral; patient 2: interhemispheric) and were chosen for their inactivity and distance from the active electrodes. The amplified LFP signals were digitized at 1,000 Hz and saved to hard disk along with stimulus markers for subsequent off-line analysis.

**Localization of cortical structures.** Each patient underwent a structural MRI scan prior to grid implantation. After implantation of the electrodes, the correct localization of the grids was verified by a CT scan. To perform the EEG source analysis using the information of the individual brain shape, electrode positions had to be determined relative to the individual brain; hence, a common coordinate system was needed for the CT and MRI scans (Talairach and Tournoux 1988) using Brainvoyager. The center of the Talairach X, Y, Z coordinate system is the anterior commissure, and the axes are as follows: X—medial-lateral direction, positive values for the right hemisphere; Y—anterior-posterior direction, positive values anterior; Z—superior-inferior direction, positive values rostral. Matching of the MRI and CT scans was achieved with the help of anatomic landmarks visible in both scans. These fiducials were the nasion, the inion, and the preauricular points. On the basis of individual electrode coordinates in Talairach space, Brain Electrical Source Analysis software (BESA 5.1.8; Scherg 1992) calculated the best-fitting ellipsoid of each subject.

The radiological location of structures on the cortical surface incorporated the results of electrophysiological studies and intraoperative observations, which included photographs. The latter observations were partially based upon the predictions of a computerized guidance system (Brainlab, Westchester, IL). The electrophysiological localization of the central sulcus was carried out by SEP N20–P20 polarity reversal, as in previous studies (Ohara et al. 2004b; Baumgärtner et al. 2010).

**Data and dipole source analysis.** For each subject and each modality of stimulation, averaged waveforms were obtained after confirmation of the reproducibility of results from each of the two recording blocks. 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 reported in this article were measured as peak latencies.

After import of the averaged LEP and SEP data into the source analysis software, data were re-referenced off-line versus average reference for calculation of the GFP (= spatial standard deviation as a function of time; Strik and Lehmann 1993). GFP is a measure of spatial variance, which collapses information from all scalp electrodes at each time point independent of the location of a particular activation maximum, thus yielding a reference-free measure of the component structure. According to the data structure of the individual patients, a time window for the analysis of the first components was chosen from onset to peak of the first GFP peak.

Since we had no a priori estimate of the number of sources needed to model activity measured from the grid electrodes, we started the fitting procedure using a regional source (RS). The RS was a set of three dipoles with the same location but mutually perpendicular orientations representing electrical activity in a small volume of cortex irrespective of the net dipole orientation. In the fitting procedure, which is purely data driven, a regional source has only 3 degrees of freedom, which makes this a robust analysis without the possible bias of a set of constraints that may be needed if multiple dipoles are fitted simultaneously.

After the location was fitted, the model was tested by orientation fits to determine whether all three components of the RS, or just one or two components, were needed to explain the data variance at the early time window (see RESULTS). If one of the three components of the RS was found to explain <5% of the data within the time window, it was deleted from the model. The quality of a fit can be estimated by the “goodness of fit” (GoF), which is the amount of data variance explained by the dipole model. The inverse of the GoF is the residual variance (RV), which is the data
not explained by the model. If our model explained <75% of the data variance in this time window, then we added more sources. Details of the fitting sequence for the LEP are given in RESULTS.

Details of the source analysis of the early SEP data are the same as those in the companion paper (Baumgärtner et al. 2010) and include the N20 from area 3B and the P22 from area 1.

RESULTS

LEP and current source density. Figure 1A, left, shows that the LEP could be recorded from different contacts on the grid over the left hemisphere in patient 1. The numbering of contacts within the grid is indicated just above the left end of
the LEP tracing, and the position of the grid relative to the left hemisphere is shown on surface maps in Fig. 1A, right. The dotted diagonal line from the upper right toward the center of the grid represents the central sulcus as identified intraoperatively and confirmed by electrophysiology. The dotted lower line (horizontal course across the grid) is the sylvian fissure, as identified intraoperatively. In this figure, negativity is upward with respect to a common reference electrode (contact 65), which is outside the sketch. Contact 8 in the upper right corner was switched off because it was noisy.

In Fig. 1, A and B, circles indicate early negative (blue) and positive (red) deflections in the 130–145 ms range; note the negativity in the upper central region (upper right of the grid), centered slightly anterior to the central sulcus (maximum negativity at contact 23), without polarity reversal. At the same time, a polarity reversal across the anterior part of the sylvian fissure can be seen (lower left of the grid), although this is not prominent on the current source density (CSD), perhaps because of the resolution of the CSD.

Figure 1B shows circles that highlight potentials in the “early” range of 130–145 ms after stimulus for patient 2. As in patient 1, there is a negativity in the upper central region (upper left of the grid), around the central sulcus, without polarity reversal across the central sulcus. This is also reflected in the CSD (Fig. 1, A and B, right). Although more channels show a negative deflection posterior versus anterior of the central sulcus, the largest amplitude can be seen anterior to the central sulcus (contact 12). A potential polarity reversal is seen across the anterior part of the sylvian fissure, and a substantial positivity can be seen above the sylvian fissure.

As described in METHODS, two additional patients (patients 3 and 4) were studied in the companion paper (Baumgärtner et al. 2010). These two patients yielded LEP responses similar to those in patients 1 and 2. In particular, the LEP revealed a surface negativity in all four patients near the central sulcus with an average latency of 148 ± 8 ms (mean ± SE) for the response to laser stimuli. However, only patients 1 and 2 yielded signals that were both “free” of noise and comprised a GFP structure having clear peaks (Fig. 2). Therefore, the dipole source analysis could only be performed in patients 1 and 2.

Source analysis. The general fitting strategy in our source analysis is based on the data as follows. The GFP in patients 1 and 2 consisted of two major peaks (Fig. 2). Both peaks were fitted in serial order so that the fit of the second GFP peak was performed with sources explaining the first peak switched on. Windows for each peak were chosen on an individual basis, as specified for each patient below. Further sources were added if the GoF was <70%. If additional sources did not explain more than an additional 5% of the data variance, they were discarded.

Figure 2A shows the final result of source analysis for patient 1. Specifically, insertion of a RS and the fit within the time window (onset to peak) of the first GFP peak (69% of peak GFP) yielded a localization near the sensorimotor cortex with a GoF of 65%. Orientation fits revealed one radial component peaking at 139 ms (Fig. 2A, left). The remaining two components explained <1% in the fit window and <4% in the whole 0–400 ms window, and were deleted from the model.

Adding a second RS resulted in a dipole located in the opercular cortex, which increased the GoF during the first GFP peak to 75% and that during the second GFP peak from 34% to 70%. The main component had an oblique orientation and a biphasic activity at 135 ms and 219 ms [GoF was increased from 21% to 51% in the whole 400-ms window (Fig. 2A)]. The final data model includes the early radial dipole (red, GFP peak at 130 ms) in the primary sensorimotor area along with activity from the opercular dipole (blue, GFP peak at 223 ms).

Figure 2B shows the result of source analysis for patient 2. Insertion of a RS and a fit within the time window of the first GFP peak (onset to peak) yielded a localization near the sensorimotor cortex with a GoF of 45% in this time window (best time point of fit 50% GoF). Orientation fits revealed one radial component peaking at 135 ms and one tangential component peaking at 211 ms. The third component explained <1% of the data and was deleted from the model.

Since the GoF was only 50%, another RS was added and fitted during the same time window. This yielded a main component with an almost radial orientation (peak activity at 145 ms). It localized in the opercular area and raised the GoF to 75% in the fit window (best time point of fit 50% GoF, 50% in whole 400 ms window; Fig. 2B). This dipole might have been expected given the LEP waveforms found in the grid channels overlaying this region (Fig. 1B).

Adding further test sources never increased the GoF of either peak by >5% (usually between 1% and 2%) or changed the angle of the dipoles by >10°. The same was true for the second GFP peak, where the highest GoF was 65–70%; adding sources did not improve the GoF.

With respect to the time window beyond 300 ms, adding further sources did not result in an improvement of the GoF by >5%. As the final test for potential “missed sources,” we applied LEP sources including early symmetrical opercular, midcingulate, and S1, as previously realized with scalp recording (Schlereth et al. 2003). The GoF never exceeded 50%, and the source waveforms did not exhibit the usual temporal sequence known from scalp recordings. Moreover, the GFP of the subdural data did not show the major late GFP peak found in scalp recordings (Fig. 3C of Schlereth et al. 2003). Probably the few channels with late activity (Fig. 1, left) did not yield enough GFP power to be recognized as relevant peaks. This may be due to the difference in cortical surface (near field) potentials and scalp far field potentials.

In summary, a S1 source was found for both patients, one with a single radial dipole (Fig. 2A, patient 1, red dipole). Patient 2 had a radial dipole and later possible tangential dipole (both red), with the second medial to the first (Fig. 2B). In addition, opercular radial dipoles were found for both patients. In Table 1, these dipole locations are compared in Talairach coordinates (Talairach and Tournoux 1988) with those for the SEP in the same patients, as reported in the companion paper (Baumgärtner et al. 2010). This table shows that sensorimotor generators of LEP are consistently medial to the SEP generators, which is consistent with EEG and MEG studies (Kanda et al. 2000; Ohara et al. 2004b; Ploner et al. 1999b, 2000, 2002).

In patient 1, the location of the early radial laser sensorimotor dipole was displaced medial, anterior, and deep to the SEP (Fig. 2A, Table 1). In patient 2 (Fig. 2B), the earliest LFP activity is explained by the radial dipole with surface negative (red dipole I) in the sensorimotor area. This dipole was slightly medial, anterior, and deep to the location of the SEP P22 dipole. This is compatible with a generator in area 3A, which is located anterior and deep to the crest of the central sulcus,
based upon anatomic atlases and cytoarchitectonic analyses of cadaveric brains (Duvernoy et al. 1991; Mai et al. 2007; White et al. 1997). The second dipole of LEPs in patient 2 was oriented tangentially with negative anterior and was located near the N20 SEP dipole, but 9 mm further medial in the X coordinate.

The surface negative orientation for the radial sensorimotor red dipole could be consistent with a source in area 3A if we make the assumption of surface negativity, unlike the SEP dipoles, which are surface positive (see Discussion and Rausell and Jones 1991a).

The later tangential dipole in patient 2 had negativity anterior and positivity posterior. This dipole is consistent with a dipole in either area 3B or area 4 (Andersen et al. 1964), based on the assumption of surface negativity or positivity, respectively. Therefore, the sources giving rise to the LEP may derive their location and orientation based upon the anatomy and physiology of areas 3A and 3B.

Fig. 2. A: final Brain Electrical Source Analysis (BESA) result of source fitting (patient 1). Global field power (GFP) and goodness of fit (GoF) on top left; source activities (in nAm) over time on bottom left. The time window is 0–400 ms after stimulus. Middle: head model views with dipole sources. Right: CSD maps at the 1st (138 ms) and 2nd (220 ms) GFP peak, with data, model and residuals that correspond to model subtracted from data. Blue: negativity; red: positivity. B: results as in A but CSD maps at right cover the 1st (141 ms) and 2nd (212 ms) GFP peaks in patient 2, as labeled.
Table 1. Location of LEP sources relative to SEP (N20 or P22) recorded in the same patients, and in Talairach X, Y, and Z coordinates

<table>
<thead>
<tr>
<th>Patient 1 (X, Y, Z)</th>
<th>Radial Source</th>
<th>Tangential Source</th>
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<tbody>
<tr>
<td></td>
<td>LEP vs. SEP (X)</td>
<td>Relative location</td>
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<tr>
<td></td>
<td>LEP vs. SEP (Y)</td>
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<td></td>
<td>LEP vs. SEP (Z)</td>
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<tr>
<td></td>
<td>LEP</td>
<td>−30, 8, 52</td>
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<tr>
<td></td>
<td>SEP</td>
<td>−52, −6, 60</td>
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<td></td>
<td></td>
<td>21 mm medial</td>
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<td></td>
<td></td>
<td>14 mm anterior</td>
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<td></td>
<td></td>
<td>8 mm deep</td>
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<td></td>
<td>LEP vs. SEP (X)</td>
<td>6 mm medial</td>
</tr>
<tr>
<td></td>
<td>LEP vs. SEP (Y)</td>
<td>3 mm anterior</td>
</tr>
<tr>
<td></td>
<td>LEP vs. SEP (Z)</td>
<td>5 mm deep</td>
</tr>
<tr>
<td>Patient 2 (X, Y, Z)</td>
<td>29, −10, 63</td>
<td>35, −12, 68</td>
</tr>
<tr>
<td></td>
<td>LEP vs. SEP (X)</td>
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<td>LEP vs. SEP (Y)</td>
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<td></td>
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<td>SEP</td>
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LEP, laser evoked potential; SEP, somatosensory evoked potential.

DISCUSSION

The present results demonstrate that both patients had an early radial dipole with surface negative (red dipole 1) anterior and deep to Brodmann area 3B, as identified by the SEP. The SEP generator has been characterized as a tangential dipole with frontal positivity and parietal negativity in the posterior wall of the central sulcus, consistent with area 3B (Allison et al. 1991; Desmedt et al. 1987; Jung et al. 2003; Kakigi 1994; Tiihonen et al. 1989; reviewed by Lee and Seyal 1998). In cadaveric human brains, cytoarchitectonic analysis reveals that the deepest part of area 3B is ~1 cm below the convexity and that area 3A is deeper still (White et al. 1997). True sagittal atlas sections demonstrate that the depth of the central sulcus in the hand area is ~1 cm anterior to the position of the central sulcus at the convexity (Duvernay et al. 1991; Mai et al. 2007). The difference in the medial lateral position of this dipole may be related to the complex folding of Brodmann area 3A and 3B cortex in the depths of the central sulcus, which commonly includes two fundi (White et al. 1997). Therefore, Brodmann area 3A is anterior and deep to area 3B, which is consistent with the location of the radial dipole of the LEP anterior and deep to the SEP dipole.

The early radial peak had superficial negativity, which seems contrary to the usual polarity of somatic sensory evoked potentials. A surface negative orientation is consistent with the termination of thalamocortical axons from neurons receiving spinothalamic inputs, which is in superficial layers of cortex in Old World monkeys (Rausell and Jones 1991a, 1991b) but perhaps not in New World monkeys (Shi et al. 1993). On the contrary, the input from neurons receiving input from the mediallemniscus terminates deeper in layers 3 and 4, and so is surface positive and deep negative (Andersen et al. 1964).

S1 has also been studied by the intrinsic optical signal in response to tactile and heat stimuli in anesthetized squirrel monkeys (Tommerdahl et al. 2002; Whitsel et al. 2000). Nociceptive heating (52°C) led to a change in optic signal in area 3A that was larger than that in response to 37°C, while the signal in areas 3B and 1 was smaller (Tommerdahl et al. 1996). Strong evidence for the involvement of area 3A in nociceptive processing comes from a recent study by the same group (Whitsel et al. 2009). In this study, 3A neuronal firing in monkeys significantly increased when temperatures in the nociceptive range were applied to the neuronal receptive field to innocuous mechanical stimuli.

The present area 4 is not a likely generator of the radial LEP dipole because it does not involve the depth of the central sulcus in cadaveric human brains (White et al. 1997). In addition, the surface negativity of LEP dipoles predicts an orientation of an area 4 tangential dipole opposite that which was observed here (Rausell and Jones 1991a). A dipole in area 6 could explain the CSD observed in Fig. 1 and the GFP in Fig. 2, but not the source analysis (Fig. 2, A and B, middle), since it would be anterior to area 4, which makes this possibility very unlikely.

Methodological considerations. The subjects described here have epilepsy with associated clinical, radiological, and electrical abnormalities and with significant blood levels of antiepileptic drugs. As described previously, the occurrence of LEP was not related to mesial temporal sclerosis (Liu et al. 2010), which is scarring of the medial temporal lobe that is associated with epilepsy (Williamson et al. 1993). The small number of subjects in this study is standard for intracranial recordings of primates including monkeys, and is offset by the high resolution of such studies.

In most reports, LEP are recorded from the scalp, where they are limited by muscle and blink artifacts, by low-pass and spatial filtering at the scalp, skull, and CSF (Cooper et al. 1965; Gevins et al. 1994; Lenz et al. 1998, 2000; Ohara et al. 2004a, 2004b, 2004c; Pfurtscheller and Cooper, 1975; Valeriani et al. 2000; Vogel et al. 2003; Wang et al. 2007), and by large interelectrode distances (Garcia-Larrea et al. 2003). We have applied subdural recordings, a technique that brings increased resolution and clarity to the study of human S1 cortical pain mechanisms (Ohara et al. 2004b; Scherg 1992). Nevertheless, we cannot exclude the possibility that our technique may not have discovered the very earliest primary evoked potential, since the number of laser stimulus repetitions had to be smaller than typical for median nerve electrical SEP in order to avoid burns. Two studies have reported slightly earlier components with special tasks or analysis procedures (Vogel et al. 2003), but our results are consistent with the conduction velocity of A-delta fibers and the general component structure of the LEP (Frot and Mauguire 2003). The recent demonstration of the feasibility of high-frequency nociceptive stimulation with EEG recording may help to equalize the imbalance of the different number of stimuli between modalities and to gain further insight into nociceptive processing (Mouraux et al. 2011).

Source analysis from subdural recordings is a refinement of source analysis techniques from scalp recordings, which improves the accuracy of the localization for scalp and subdural recordings (Zaslansky et al. 1995). Our prior study of parasympathetic sources was carried out on potentials arising from noci-
ceptual and auditory stimuli in patients with implanted grids (Legrain et al. 2005, 2011; Mouraux and Iannetti 2009). The cortical auditory evoked potentials (AEP) were located precisely over Heschel’s convolution, and cortical LEP were later confirmed by depth recordings (Ohara et al. 2004a, 2004b, 2004c; Kobayashi et al. 2009), thus validating source analysis from subdural recordings.

Our protocol did not test the extent to which LEP generators are specific for nociceptive processing, either for differences versus nonnociceptive somatic sensory stimuli or for the effects of attention and stimulus salience (Hamalainen et al. 1990; Hashimoto et al. 1998, 1999; Jones and Friedman 1982; Jones et al. 1982; Kanda et al. 2000; Ploner et al. 1999b, 2000, 2002; Schlereth et al. 2003; Timmermann et al. 2001). Although our previous studies have included attention tasks and nonnociceptive stimuli (Ohara et al. 2004b), that approach is beyond the scope of this paper.

Putative tangential sensorimotor generator. The early radial dipole in patient 2 is followed, in patients 1 and 2, by activity from a dipole that is located superficially medial to the SEP dipole, with negativity anterior and positivity posterior. The longer latencies of the putative tangential LEP dipole are consistent with single-neuron recordings from thalamic nuclei receiving spinothalamic terminals (Kenshalo and Isensee 1983). This putative tangential peak may have been missed in patient 1, in whom the contacts extended <1 cm behind the central sulcus (Fig. IA), while those of patient 2 extended between 2 and 5 cm behind the central sulcus (Fig. IB). The paucity of electrodes posterior to the central sulcus may have limited our ability to identify a tangential dipole in patient 1.

The location and orientation of this putative tangential LEP dipole in patient 1 are similar to those of the SEP but of opposite polarity. In the companion paper (Baumgärtner et al. 2010), the distribution of the tangential dipole of the SEP was consistent with the generator in area 3B. Recent MEG or EEG source analysis studies of LEPs have identified a tangential current source (MEG current dipole equivalent) in the S1 region like the LEP dipole found here (Fig. 2B) (Kanda et al. 2000; Ploner et al. 1999b, 2000, 2002; Schlereth et al. 2003; Timmermann et al. 2001).

The polarity of the putative tangential dipole with negativity anterior and positivity posterior was consistent with source analyses of scalp-recorded LEP (Schlereth et al. 2003; Tarkka and Treede 1993) but was opposite to the polarity of SEP N20, which had negativity posterior. This is consistent with a surface negative source of the LEP in area 3B, as described above. Studies in anesthetized monkeys have demonstrated that nociceptive heat may result in the activation of area 3B (Bushnell et al. 1999), area 1, or the border zone between areas 1 and 3B (Apkarian et al. 2005; Hofbauer et al. 2001; Lenz et al. 2010). S1 neurons with selective responses to nociceptive tooth pulp stimuli have also been reported in awake monkeys (Price 2000).

It may be that the putative tangential peak is related to direct activation of S1 by the input from thalamocortical cells receiving input from the spinothalamic tract (Liu et al. 2011a). However, area 4 is an unlikely generator of the putative tangential LEP dipole because the orientation of such a dipole is opposite to that expected for superficial nociceptive thalamocortical terminations.

Current models suggest that S1 has a role in the sensory discriminative dimension of pain (Apkarian et al. 2005; Lenz et al. 2010; Price 2000), and perhaps a pivotal role. This latter suggestion may be consistent with a recent report demonstrating that during directed attention human S1 exerts a driver role in medial frontal and parasympathetic cortex following a laser stimulus, although nonpainful control was not included in that study (Liu et al. 2011a). This causal influence would be an epiphenomenon if S1 were not essential for pain perception. This seems unlikely since lesions of S1 can produce isolated diminution of the sensory discriminative dimension (Ploner et al. 1999a; Veldhuijzen et al. 2009), although there can be difficulties in the interpretation of somatic sensory findings following parietal lobe lesions (Hoogenraad et al. 1994; Legrain et al. 2011; Liu et al. 2011b; Mouraux and Iannetti 2009).

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DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

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