Mapping of Early and Late Human Somatosensory Evoked Brain Potentials to Phasic Galvanic Painful Stimulation

Claudio Babiloni,^{1,2*} Fabio Babiloni,¹ Filippo Carducci,¹ Febo Cincotti,^{1,2}
Fabrizio Rosciarelli,¹ Paolo Maria Rossini,³ Lars Arendt-Nielsen,⁴
and Andrew CN Chen⁴

¹Dipartimento di Fisiologia Umana e Farmacologia, Università di Roma "La Sapienza," Roma, Italy

²A.Fa.R. CRCCS—Dipartimento di Neuroscienze, Osp. FBF Isola Tiberina, Roma, Italy

³IRCCS "S. Giovanni di Dio," Brescia, Italy

⁴Center for Sensory-Motor Interaction, Human Brain Mapping and Cortical Imaging Laboratory, Aalborg, Denmark

Abstract: In the present study, we modeled the spatiotemporal evolution of human somatosensory evoked cortical potentials (SEPs) to brief median-nerve galvanic painful stimulation. SEPs were recorded (−50 to +250 ms) from 12 healthy subjects following nonpainful (reference), slight painful, and moderate painful stimulations (subjective scale). Laplacian transformation of scalp SEPs reduced head volume conduction effects and annulled electric reference influence. Typical SEP components to the galvanic nonpainful stimulation were contralateral frontal P20-N30-N60-N120-P170, central P22-P40, and parietal N20-P30-P60-P120 (N = negativity, P = positivity, number = latency in ms). These components were observed also with the painful stimulations, the N60, N120, P170 having a longer latency with the painful than nonpainful stimulations. Additional SEP components elicited by the painful stimulations were parietomedian P80 as well as central N125, P170 (cP170), and P200. These additional SEP components included the typical vertex negative-positive complex following transient painful stimulations. Latency of the SEP components exclusively elicited by painful stimulation is highly compatible with the involvement of A delta myelinated fibers/spinothalamic pathway. The topography of these components is in line with the response of both nociceptive medial and lateral systems including bilateral primary sensorimotor and anterior cingulate cortical areas. The role of attentive, affective, and motor aspects in the modulation of the reported SEP components merits investigation in future experiments. *Hum. Brain Mapping* 12:168–179, 2001. © 2001 Wiley-Liss, Inc.

Key words: phasic painful stimulation; EEG, median-nerve somatosensory-evoked potentials (SEPs); surface Laplacian; human cerebral cortex

INTRODUCTION

Human nociception is a multidimensional phenomenon involving separate sensory-discriminative, affective-motivational, and cognitive aspects, which would be subserved by a distributed brain system [Melzack and Casey 1968; Coghill et al., 1994]. Positron emission tomography has revealed that the major brain structures involved in tonic painful information processing are the contralateral insula and anterior cingulate cor-

Contract grant sponsors: Danish National Research Council, Italian Ministry of Health, and Association Fatebenefratelli for the Research (AFaR).

*Correspondence to: Dr. Claudio Babiloni, Dipartimento di Fisiologia Umana e Farmacologia, Sezione di EEG ad Alta Risoluzione, Università degli Studi di Roma "La Sapienza," P.le Aldo Moro 5, 00185 Rome, Italy. E-mail: claudio.babiloni@uniroma1.it

Received for publication 7 April 2000; accepted 23 October 2000

tex, the bilateral thalamus and premotor cortex, and the cerebellar vermis [Casey, 1999]. On the other hand, functional magnetic resonance imaging has shown controversial results on the involvement of primary sensorimotor cortex (M1-S1) and secondary somatosensory cortex in the nociceptive information processing [Davis et al., 1995; Porro et al., 1998; Becerra et al., 1999; Ploghaus et al., 1999]. Remarkably, the long time resolution (seconds to minutes) of these techniques is insufficient for the study of transient brain activity related to a brief painful stimulation. In contrast, electroencephalography (EEG) and magnetoencephalography possess a millisecond time resolution suitable for such a purpose. However, the spatial resolution of these techniques (centimeters) is lower than that (millimeters) of the functional magnetic resonance imaging or positron emission tomography.

Somatosensory evoked cortical potentials (SEPs) following brief galvanic painful stimulations present a typical vertex (Cz of 10–20 electrode system) negative-positive complex, which occurs approximately 100–300 ms after the noxious stimulation. Modal specificity of this complex is suggested by a certain correlation between the amplitude of the vertex potential and the pain magnitude/analgesics administration [Chudler and Dong, 1983; Chen, 1993; Bromm and Lorenz, 1998]. Noteworthy, the physiological relevance of these findings is reduced by the fact that scalp potentials are affected by head volume conductor and electrode reference effects. In this regard, surface Laplacian derivation is a mathematical spatial high-pass filter that removes both head volume conductor and electrode reference effects [Nunez, 1995]. In some cases, the surface Laplacian estimate permits the modeling of discrete cortical areas generating event-related scalp potentials.

In the present study we investigated the spatiotemporal evolution of human SEPs related to brief median-nerve galvanic painful stimulation (SEPs to nonpainful stimulation as a reference). The median nerve stimulation served to induce a cortical response largely studied in nonpainful condition. Two levels of galvanic painful stimulation (slight and moderate painful levels) were used to evaluate the specificity of such stimulations [Bromm and Meyer, 1984]. With respect to previous studies, the use of a large amount of single trials (600) to painful stimulations could provide a good signal-to-noise ratio for the analysis of short and middle latency SEPs. Furthermore, the surface Laplacian estimate enhanced the spatial information content of these potentials (multi-electrode EEG recordings). A main issue of interest was the timing of the participation of M1-S1 and midline cortex (including ante-

rior cingulate areas) to nociceptive processes. These areas would be mainly involved in the sensory-discriminative and affective-motivational analysis of the painful stimulation, respectively.

METHODS

Twelve young (age: 26.8, ± 5.2 years), healthy male volunteers participated to the present study. All subjects gave their written informed consent according to the Declaration of Helsinki and could request an interruption of the investigation at any time. The local institutional ethics committee approved the general procedures. During the EEG recording, participant subjects were seated in a comfortable reclining armchair placed in a dimly lit, sound-damped and electrically shielded room.

During the experimental sessions, the median nerve was stimulated at the left wrist (3 Hz) with 0.2 ms square wave duration. Experimental design included three levels of painful stimulation intensity (nonpainful, slight painful, and moderate painful levels), according to a subjective scale. The stimulation levels were determined by a series of increasing and decreasing stimulus intensities at the beginning of each recording block. The painfulness of the stimuli was rated verbally by the subjects on a numerical scale ranging from 0 (no sensation) to 10 (pain tolerance threshold). In this scale, the values of 2 (painless thumb muscle twitch) and 4 (slight pain) indicated the motor and pain thresholds, respectively. Furthermore, the value of 6 (moderate pain) corresponded to a pain level proportionally distributed between the values of 4 and 10. The mean stimulus intensities for the nonpainful, slight painful, and moderate painful stimulations were of 7.9 (± 3.6), 17.6 (± 5.9), and 25.8 (± 7.8) mA, respectively. These mean and $\pm$ SD values indicate that in few subjects, the painful stimulus evoking slight painful sensations had about the same magnitude of the painful stimulus evoking moderate painful sensations in other subjects. Such a little overlap in the painful stimulus intensity suggests that the differences in the SEPs following the slight and moderate painful stimulations depended more on the subjective stimulus perception than on the absolute magnitude of the painful stimulation.

To maintain a stable level of vigilance and to minimize the effects of habituation, the blocks of the galvanic nonpainful and painful stimulations were randomized across subjects. Each participant was given a brief training session in which he learned to stare at a visual fixation point and to minimize blinking and eye movements during the recording block.

SEPs were recorded (NeuroScan System; band pass: 0.05–500 Hz, sampling rate: 2,000 Hz) from 31 electrodes. The electrodes were placed according to an augmented 10–20 system, which included 19 standard electrodes plus 12 additional uniformly spaced electrodes. Linked ears served as an electrical reference. Electrode impedance was kept lower than 5K Ohm. Furthermore, an electro-oculographic channel was used to monitor eye movements and blinking. Since subjects did not perform involuntary hand motor response following the galvanic stimulations (apart stimulus-locked thumb muscle twitch) during the preliminary experimental sessions, no electromyographic channel was used during the EEG recording. The experimenters controlled the occurrence of poststimulus movements during the EEG recordings by visual inspection. Acquisition time for the EEG and electro-oculographic data was set from 50 ms before to 250 ms poststimulus. About 600 EEG trials were collected for each stimulus condition. EEG trials contaminated by blinking, eye movements, and/or other artifacts were rejected offline. Artifact-free trials of SEPs were averaged separately for each stimulation condition. Of note, subjects' selection, EEG recordings, and the single trial rejection were performed at the University of Aalborg (Denmark), while the data analysis was performed at the University of Rome (Italy).

To enhance spatially the individual averaged SEPs, surface Laplacian estimate was performed by 3D spline function over a spherical scalp surface model. In some cases, the Laplacian values on the border electrodes were zeroed because of unreliability of the spline Laplacian estimate for these electrodes. Further details on the "lambda" regularization of the spline surface Laplacian estimate have been previously reported [Babiloni et al., 1996, 1998]. Latency and amplitude of the SEP components were measured in individual data sets for each stimulation condition. Peak latency of the SEP components was measured with respect to the time of the stimulation (zerotime). Peak amplitude of these components was referenced to the prestimulus baseline.

Across-subjects grand averaging was performed on individual SEP distributions (measured peak values at 31 electrodes) rather than averaging individual data sets with reference to zero time (standard grand averaging). For example, the grand average of P20-N20 SEP was computed from the potential distribution of subject 1 at +19.5 ms (individual P20-N20 peak), the potential distribution of subject 2 at +20.5 ms (individual P20-N20 peak), etc. Compared to the standard grand averaging technique, the averaging of individual potential distributions allowed removal of time

jitter of individual SEP peaks from the grand averaged data. Of note, this was particularly important given that SEPs elicited by painful stimuli might present a high intersubject variability in latency. Nevertheless, we checked the level of intersubject variability in SEP amplitude by a topographic color mapping of the standard error (gray scale including 256 hues).

Amplitude of the SEPs following the nonpainful and painful stimulations was compared with a two-step statistical procedure. Maximum differences in latency and amplitude SEP values were selected with a preliminary descriptive topographical data analysis based on the color mapping of statistical *t* values (color scale including 256 hues). While, a Bonferroni-corrected paired *t* testing was performed at most responsive electrodes for the final evaluation ($P < 0.05$).

Amplitude 256-color maps of the SEP mean, standard error, and *t* statistics were calculated on a 3D quasi-realistic head model by a spline interpolating function [Babiloni et al., 1995]. This model was constructed based on the magnetic resonance data of 152 subjects digitized at Brain Imaging Neurologic Institute of Montreal (SPM96).

RESULTS

The reliability of centromedian (Cz, 10–20 system) waveforms of spatially enhanced SEPs in a representative subject is illustrated in Figure 1. The centromedian SEP waveforms in the first and second halves of the experimental moderate painful condition were quite consistent. Only sporadically (3 out of 12 subjects), a middle-latency negative SEP component was larger in amplitude during the second than the first half of the moderate painful stimulation, possibly due to slight sensitization effects. On the other hand, the subtraction waveform of centromedian SEPs to the moderate painful minus nonpainful stimulation disclosed the typical SEP negative-positive complex commonly observed after a painful stimulation [Bromm and Lorenz, 1998].

Representative individual waveforms of spatially enhanced SEPs following the nonpainful (thin traces) and moderate painful (thick traces) stimulations are depicted in Figure 2. For the nonpainful condition, maximum potential amplitude was computed at contralateral frontal (F4 electrode, 10–20 system), central (C4 electrode), and parietal (P4 electrode) scalp locations. In all subjects, spatial enhancement of the SEPs cancelled potentials peaking about 14–18 ms (P14, N18) poststimulus. The SEPs following the nonpainful stimulation presented a sequence of typical peaks having a mean latency of about 20, 22, 30, 40, 60, 120, and

Figure 1.

Reliability of centromedian (Cz, 10–20 system) waveforms of spatially enhanced somatosensory evoked potentials (SEPs) to galvanic painful stimulation in a representative subject. Stimulation consisted of a brief galvanic shocks delivered at the left wrist in correspondence with median nerve locations. Experimental design included three levels of painful stimulation intensity (non-painful, slight painful, and moderate painful levels), according to a subjective scale. The centromedian SEP waveforms are shown averaging trials of the first (1–300 trials) and second (301–600 trials) halves of the experimental painful conditions. As a reference, the subtraction waveform of centromedian SEPs to the moderate painful minus nonpainful stimulation is also shown.

170 ms poststimulus. Based on their topography, polarity, and latency, these peaks were labeled frontal P20–N30–N60–N120–P170, central P22–P40, and parietal N20–P30–P60–P120. These peaks were also observed following the moderate painful stimulation. In addition, the SEPs following the painful stimulations showed further peaks. In all subjects, these additional peaks had a latency of about 80, 125, 170, and 200 ms poststimulus and were labeled parietal P80 and central N125–P170–P200. Table I reports the across-subjects mean latency and standard error of the standard SEP components following the nonpainful and painful conditions. Statistical analysis showed significant later peaks of frontal N60, N120, and P170 in the moderate painful than nonpainful conditions ($P < 0.01$). The across-subjects mean latency and standard error of the SEP components following the painful stimulations are given in Table II.

The across-subjects amplitude color maps of the spatially enhanced SEP components following the

nonpainful stimulation (P20–N20, P22, N30–P30, P40, N60, N120, and P170) are shown in Figure 3. As a reference, the maps of the corresponding SEP components following the slight and moderate painful stimulations were also shown. For the nonpainful stimulation, the P20–N20 map consisted of contralateral dipolar frontal positivity/parietal negativity (i.e., similar amplitude of the negative and positive values). Compared to the N20–P20 map, the N30–P30, N60, and N120 maps showed a dipolar pattern with similar spatial distribution but opposite polarity. On the other hand, the P22 and P40 maps were represented by a mainly unipolar contralateral central positivity within a background negativity of low amplitude (field-based color scale magnified this background negativity). The unipolar nature of this field is suggested by the fact that the contralateral central positivity was much higher in amplitude than the concomitant background negativity. Finally, the P170 map was characterized by circumscribed frontocentral positivity contralateral to

Figure 2.

Most representative waveforms of spatially enhanced SEPs to the nonpainful (thin traces) and moderate painful (thick traces) stimulations in the representative subject.

TABLE I. Across subjects mean latency and standard error of the standard SEP components to the non-painful and painful stimulations

STANDARD SEPs LATENCY (ms)			
	No pain	Slight pain	Moderate pain
P20-N20	20.5 ± 0.2	20.5 ± 0.2	20.2 ± 0.2
P22	23.0 ± 0.5	22.9 ± 0.5	22.8 ± 0.4
N30-P30	30.9 ± 1.4	29.9 ± 1.2	30.2 ± 1.3
P40	44.4 ± 3.4	42.7 ± 3.7	42.6 ± 3.6
N60-P60	67.2 ± 3.1	79.1 ± 2.9	79.7 ± 3.7
N120-P120	110.5 ± 6.5	146.1 ± 3.9	152.7 ± 5.6
P170	152.6 ± 4.3	182.5 ± 6.5	187.9 ± 5.6

the stimulation. A similar topography was observed in the maps of the corresponding SEPs to the slight and moderate painful stimulations. As unique exceptions, the N120 and P170 maps (painful stimulations) presented a strong negativity in the frontocentral median

TABLE II. Across-subjects mean latency and standard error of specific SEP components to painful stimulations

PAIN SEPs LATENCY (ms)		
	Slight pain	Moderate pain
P80	81.2 ± 3.5	80.8 ± 2.5
N125	121.5 ± 2.9	124.4 ± 2.7
cP170	165.2 ± 3.5	169.1 ± 2.6
P200	181.2 ± 7.5	181.2 ± 6.4

area and additional positivity in the centromedian or ipsilateral central areas, respectively.

The across-subjects amplitude color maps of the specific SEP components following the slight and moderate painful stimulations (P80, N125, cP170, P200) are illustrated in Figure 4. As a reference, the maps of SEPs to the nonpainful stimulation were also shown at the same latency of the SEP components following the painful stimulations (P80, N125, cP170,

Figure 3.

Across-subjects amplitude color maps of the spatially enhanced SEP components to nonpainful stimulation (P20-N20, P22, N30-P30, P40, N60, N120, and P170). As a reference, the maps of corresponding SEPs to the slight and moderate painful stimulations are also shown. The maps were calculated on a 3D “quasi-realistic” head model by a spline interpolating function. This model was constructed based on the magnetic resonance data of 152 subjects

digitized at Brain Imaging Neurologic Institute of Montreal (SPM96). Color scale: for each map, maximum negativity (-) and positivity (+) values ($\mu\text{V}/\text{cm}^2$) are coded in white and violet, respectively. The actual maximum negative (-) and positive (+) values ($\mu\text{V}/\text{cm}^2$) of each SEP component are reported under the corresponding color map.

Figure 4.

Across-subjects amplitude color maps of the spatially enhanced specific SEP components to the slight and moderate painful stimulations (P80, N125, cP170, P200). As a reference, the maps of SEPs to nonpainful stimulation are also shown at corresponding latencies. Color scale: for each map, maximum negativity (-) and positivity (+) values ($\mu\text{V}/\text{cm}^2$) are coded in white and violet, respectively. The actual maximum negative (-) and positive (+) values ($\mu\text{V}/\text{cm}^2$) of each SEP component is reported under the corresponding color map.

P200). Remarkably, the P170 maps (Fig. 3) and the cP170 maps (Fig. 4) were computed at different latencies and were then diverse in topography. In fact, the P170 maps (Fig. 3) were computed on the basis of the latency of the corresponding SEP component following the nonpainful stimulation. Whereas, the computation of the cP170 maps (Fig. 4) was based on the latency of the corresponding SEP component following the painful stimulations. With respect to the SEPs following the nonpainful stimulation, the P80 maps (painful stimulations) showed an extension of the parietal positivity toward parietomedian areas and the N125 maps (painful stimulations) an extension of the midline negativity towards centromedian areas. The cP170 and P200 maps (painful stimulations) were characterized by a strong bilateral central and centromedian positivity.

Figure 5 plots the standard error (gray maps) of the standard SEP components (P80, N125, cP170, P200) induced by the painful stimulations. The color black codes standard-error values equal to across-subjects mean values (100%). Thanks to the grand averaging technique used (see Methods), the standard-error values of the SEPs following the painful stimulations were globally much lower than 100%. The strongest values of the standard error were computed at the long latencies.

T-testing color maps of the SEP components following the painful stimulations (P80, N125, cP170, P200) are depicted in Figure 6. These maps plot the results of the explorative statistical comparison regarding the nonpainful vs. moderate painful conditions and slight vs. moderate painful conditions. The statistical t maps showed that the painful stimulation induced a statis-

Figure 5.

Standard error gray maps of the spatially enhanced standard pain-induced (P80, N125, cP170, P200) SEP components. For each map, the color black coded standard error values equal to across-subjects mean values (100%) reported in the maps of Figure 4.

tically significant increase of the SEP amplitude. Compared to the SEPs following the nonpainful stimulation, the painful stimulation P80 maps presented statistically significant parietomedian positivity. Fur-

thermore, the painful stimulation N125 maps were characterized by a statistically significant negativity in the ipsilateral central area. Finally, the painful stimulation P170 and P200 maps indicated a statistically significant bilateral central positivity. The comparison between SEPs following the slight and moderate painful stimulations resulted in *t* values lower than those computed for the comparison nonpainful vs. moderate painful stimulations. However, there were statistical differences of the SEPs following the slight vs. moderate painful stimulations. With respect to the slight painful stimulation, the moderate painful stimulation increased the N125 in the ipsilateral central area. Furthermore, the moderate painful stimulation increased the P80, cP170, and P200 in the parietal or bilateral central areas. Final *t*-statistics at responsive electrodes of the statistical *t*-maps confirmed the significance of these preliminary results (Bonferroni corrected $P < 0.05$).

DISCUSSION

In the present study, the detailed spatiotemporal evolution of human SEPs following brief painful median-nerve galvanic stimulations was modeled. Typical SEP components following the nonpainful stimu-

Figure 6.

T-testing color maps of the spatially enhanced SEP components to the painful stimulations (P80, N125, cP170, P200). Such an explorative statistical comparison regarded amplitude of SEPs to the nonpainful vs. moderate painful conditions as well as to the slight vs. moderate painful conditions. Color scale: maximum negative (-) and positive (+) *t* values are coded in white and violet, respectively. Both negative (-) and positive (+) *t* values indicate increased amplitude of the SEPs to the moderate painful stimulation with respect to the nonpainful (first row) and slight painful (second row) stimulations. The actual maximum negative (-) and positive (+) *t* values of each SEP component are reported under the corresponding color map.

lation (reference) were contralateral frontal P20-N30-N60-N120-P170, central P22-P40, and parietal N20-P30-P60-P120. These components were also observed following the painful stimulations, the N60, N120, P170 having a longer latency following the painful than nonpainful stimulations. Additional SEP components following the painful stimulations were the parietomedian P80 as well as the central N125, cP170, and P200. These additional SEP components included the typical vertex negative-positive complex following a transient painful stimulation [Chen and Chapman, 1980; Dowman and Darcey 1994; Daum et al., 1995].

Methodological remarks

The present results had to be carefully discussed with respect to the issue of specificity of galvanic painful stimulation. Indeed, a routine transcutaneous technique such as median nerve stimulation might exhibit poor nociceptive specificity [Bromm and Lorentz, 1998]. In contrast, the use of CO₂ laser beam would have offered a highly specific stimulation of spinothalamic pathways [Arendt-Nielsen, 1994; Chen et al., 1998]. However, the thermal stimulation of nociceptors by CO₂ laser beam affects diversely A delta myelinated fibers having different heat threshold, readiness to respond, and sensitization time [Meyer et al., 1994]. This may reduce the number of pain-sensitive fibers excited synchronously and might smooth in time the SEPs.

Compared to the CO₂ laser beam, the galvanic stimulation acts directly on the nerve trunk with negligible influence of receptors. This reduces trial-to-trial jitter due to mechanical-chemical-electrical transduction of the impulse. Furthermore, the use of the nonpainful control condition as a reference paired all nonspecific variables related to muscle A alpha fiber, as reflected by the early (i.e., <50 ms) standard SEP components. In particular, increased amplitude of the SEPs following the galvanic painful stimulations would not be due to an unpaired influence of reflex muscle contractions during the nonpainful and painful conditions (i.e., this factor would have caused "gating" or reduced SEP amplitude to painful stimulations). Finally, the method of galvanic painful stimulation is very suitable for clinical application, although it is less nociceptive-specific than CO₂ laser beam. In fact, the galvanic painful stimulation is very easy to perform, does not require sophisticated technology or extra-trained technicians, is available at most clinics, and produces scalp potentials whose cortical sources have been largely studied in the reference condition (nonpainful stimulation).

The reasons indicating the reliability of the present results can be summarized as follows. First, the galvanic stimulation was carefully based on a subjective scale to guarantee a stable experience of the slight and moderate painful stimulations. Second, our grand averaging technique minimized the temporal jitter due to intersubject latency variability of SEP components to painful stimulations. Third, the painful stimulations disclosed the typical vertex negative-positive complex observed in previous studies using highly specific painful stimulations (i.e., CO₂ laser beam) [Bromm and Lorentz, 1998]. Although this complex could be related not exclusively to nociceptive processes, we did not observe it following the galvanic nonpainful stimulations. Fourth, the magnitude of the SEP components following the painful stimulations increased with the augmented magnitude of the painful stimulation (slight vs. moderate painful stimulation levels).

In the present study, the "standard" SEP components following the nonpainful and painful stimulations had similar amplitude, suggesting that the painful stimulations were not so specific to spare nerve fibers mediating tactile sense and arm proprioception. The only effect of the galvanic painful stimulation would be a longer latency of the standard SEP components N60, N120, P170. Plausibly, this was due to the overlapping of the "late" SEP components resulting from the contribution of myelinated A delta fibers, which have a conduction velocity slower than A alpha and beta fibers subserving the tactile sense and arm proprioception. The role of nociceptive unmyelinated C fibers was negligible, as a result of a very slow conduction velocity.

The modeling of the SEP cortical sources

In the present study, the Laplacian topography was used for the first time to model the spatiotemporal evolution of human SEPs following a brief painful median-nerve galvanic stimulation. However, the modeling of the SEP cortical sources requires caution even if we used the surface Laplacian estimate technique. In fact, cortical generators of SEPs could not always underlie scalp potential maxima. There is a general agreement that frontal-parietal P20-N20 is not generated by sources in the frontal and parietal cortical areas but by a tangentially oriented source buried into the parietal central sulcus cortex (area 3b) contralateral to the stimulation. This cortical area would participate also in the generation of the frontal-parietal N30-P30 [Allison et al., 1991] with a possible concomitant participation of contralateral primary [Waberski et al., 1999] and nonprimary frontal [Urbano et al.,

1998; Rossini et al., 1999] cortical areas. On the other hand, the contralateral central P22 and P40 would have a maximum over the precentral gyrus [Desmedt et al., 1987], but its main source would be located in the postcentral (area 1) gyrus [Allison et al., 1991]. The cortical sources of the SEP components following N30-P30 are a matter of debate, as they would be formed by a complex pattern of radial and tangential cortical generators. In light of these issues, one could not attribute reliably the SEPs showing maxima in the frontal or parietal areas to sources located in the frontal or parietal cortical areas. For example, frontal N60 and N120 are associated with a parietal positivity, which would indicate a possible contribution of a tangential source within the central sulcus cortex contralateral to the stimulation.

A precise localization procedure sensitive to both tangential and radial cortical sources (including those in the nonprimary frontal cortex during the N30, i.e., supplementary motor area or SMA) would have required sophisticated high-resolution EEG techniques, which comprise a higher spatial sampling (i.e., up to 128 channels) and linear inverse estimate based on realistic head and source space modeling. However, it must be stressed that even the spatial details of the high-resolution EEG technique (about 2.5 cm) are insufficient to discriminate the activity of contiguous cortical areas, such as the contralateral vs. ipsilateral SMAs, the SMA-proper vs. anterior SMA, the anterior cingulate cortex vs. SMA, the several premotor subareas, the several posterior parietal (PP) subareas, the premotor vs. M1-S1, and the M1 vs. S1 [Nunez, 1995]. Notably, possibly relevant generators of SEPs following painful stimulations such as secondary somatosensory area and insula cortex [Kitamura et al., 1995] were not discussed here. In fact, surface Laplacian estimate is not fully reliable when computed at the border electrodes of the montage such as the temporal ones (roughly overlying these cortical areas of interest). Spatial information available around electrodes is insufficient for such a purpose [Nunez, 1995]. Finally, it should be stressed that deep subcortical sources cannot be inferred from Laplacian topography, as the electrical signals coming from these sources are strongly attenuated by the Laplacian derivation [Nunez, 1995].

The modeling of brain electromagnetic activity with dipole localization techniques would have not solved all source localization issues. A fully appropriate application of the dipole localization technique would require a priori knowledge on the number of the underlying generators. In previous EEG and/or magnetoencephalography studies, two [Namiki et al., 1996;

Jousmaki and Forss, 1998; Arendt-Nielsen et al., 1999], three [Franssen et al., 1992; Cakmur et al., 1997], four [Kakigi, 1994; Kunesch et al., 1995], five [Srisa-an et al., 1996; Valeriani et al., 1998], six [Buchner and Scherg, 1991], and even ten dipoles [Miltner et al., 1994] have been used to account for the brain activation evoked by painful stimulation. In this regard, recent studies on laser-evoked intracranial EEG potentials during neurosurgery have been also contradictory in that unclear conclusions were drawn on the activation of bilateral secondary somatosensory [Frot et al., 1999] and midline cingulate areas [Lenz et al., 1998]. Even with sophisticated source localization techniques, several issues on the generators of SEPs elicited by painful stimulations would have remained open.

SEP components elicited by galvanic painful stimulations

The original and striking results of the present study regarded the specific SEP components to the painful stimulations (P80, N125, cP170, and P200) that were not observed following the nonpainful stimulation. The parietal lateral and median positivity induced by the painful stimulation P80 showed a negative frontal counterpart contralateral to the stimulation, which would indicate a complex pattern of underlying tangential and radial cortical generators. At the same latency, a frontal negativity and parietal positivity complex was also detected following the nonpainful stimulation (i.e., transition from N60 to N120). Thus, the only spatial component of the P80 specific for painful stimulation would be the parietomedian positivity. Plausibly, this parietal positivity could be related to increased spatial attention focused on the stimulated arm region following the painful stimulations. A putative source of the parietomedian P80 might be located in the PP, which receives peripheral somatosensory information from S1 (area 2) and secondary somatosensory area. The PP receives also central motor information from M1, SMA, and dorsal premotor cortex [Wise et al., 1997]. In this network, secondary somatosensory cortex would be prone to the effects of task-specific attention by increased synchronicity of neuronal firing [Steinmetz et al., 2000]. Finally, the PP receives visual information from parieto-occipital cortex [Wise et al., 1997]. From a physiological point of view, it can be speculated that the P80 induced by painful stimulation represents the "alerting" of cortical neuronal ensembles combining intra- and extrapersonal space information in preparation for an appropriate motor response. Such an "alerting process" would occur even if the subjects were asked

to perform no poststimulus motor response. Consistently, previous SEP studies using low-resolution EEG technique (i.e., no Laplacian derivation) have shown that spatial attention toward the stimulated territory could enhance specifically middle-latency positivity with no marked changes in the scalp distribution [Desmedt et al., 1983; Desmedt and Tomberg 1989; Garcia-Larrea, 1991]. Nevertheless, cerebral blood flow imaging and neurophysiological data have demonstrated that attention is neither a property of a single brain area nor a property of the entire brain [Posner et al., 1984, 1988]. Enhancement of attended or suppression of unattended sensory stimuli would depend on the task and brain area studied within an anterior and posterior attention neuroanatomical systems [Posner and Dehaene, 1994].

The N125 following the painful stimulations consisted of a strong negativity in the ipsilateral central and in the centromedian areas, which would model the activation of radial cortical generators located in the ipsilateral M1-S1 and in the anterior cingulate cortex (of note, spatial resolution of EEG technique did not allow a reliable discrimination of anterior cingulate and SMA responses). Importantly, the negativity was stronger in amplitude also over the modeled contralateral M1-S1 following the painful than nonpainful stimulations. However, the difference of the modeled contralateral M1-S1 responses did not reach the statistical significance. The lack of the statistical significance would be due to the fact that in contrast to the modeled ipsilateral M1-S1, the modeled contralateral M1-S1 was active following both the nonpainful and moderate painful stimulations. Plausibly, the painful stimulation N125 would reflect the active information processing within M1-S1 and anterior cingulate cortex. This area would be part of the lateral and median nociceptive systems, which are mainly devoted to the analysis of the sensory-discriminative and affective-motivational components of painful information processing, respectively [Treede et al., 1999]. Several studies have demonstrated a somatotopic pain representation in S1 [Lamour et al., 1983; Kenshalo and Willis, 1991]. On the other hand, perceived intensity and unpleasantness of pain were both related to painful stimulus intensity [Rainville et al., 1992], which might be encoded by anterior cingulate cortex [Sikes and Vogt, 1992]. The anterior cingulate cortex would be also implicated in the integration of affect, cognition, and response selection [Devinsky et al., 1995]. Finally, an activation of the anterior cingulate cortex following painful stimulation has been evidenced by several positron emission tomography [Svensson et al., 1997]

and SEP studies [Tarkka and Treede, 1993; Bromm and Chen, 1995].

The N125 was followed by the cP170 and P200 (painful stimulations), which were characterized by a strong positivity in the bilateral central areas and in the centromedian area. The topography of the cP170 and P200 is in line with the activity of radial cortical generators located in the M1-S1 of both sides and in the anterior cingulate cortex. From a functional point of view, these positive potentials might point to cortical controlled information processing for the inhibition of irrelevant somatosensory reafferent analysis or involuntary motor acts. This is consistent with previous evidence of an activation of the M1-S1 or anterior cingulate cortex following painful stimulation, independent of explicit motor tasks [Talbot et al., 1991; Coghill et al., 1994].

The hypothesized inhibitory meaning of the cP170 and P200 (painful stimulations) agrees with a large amount of previous evidence. There is a large consensus that negative event-related potentials indicate enhanced excitability of neural networks (i.e., preparatory state for cerebral processing), whereas late positive event-related potentials are supposed to reveal decreased excitation (i.e., disfacilitatory state of neural networks) [Birbaumer et al., 1990]. Accordingly, it was observed that reaction time delayed when concomitant strong frontal positive event-related potentials were detected [Woodward et al., 1991]. Furthermore, a more pronounced fronto-central than parietal positivity was found during no-go than go trials [Gevins et al., 1989]. Finally, amplitude of late positive event-related potentials reflected inhibition of a motor response such as the startle reflex, a whole-body flexor response (including eye blink) to external stimuli [Schupp et al., 1994].

CONCLUSION

For the first time, the present study modeled the detailed spatiotemporal evolution of human SEPs following brief painful median-nerve galvanic stimulation. Typical "standard" SEP components were observed also following painful stimulations (i.e., slowed down at middle-long latency). As original findings, specific SEP components to nociceptive stimulation were described (P80, N125, cP170, P200). They spanned middle and long latency poststimulus periods and were compatible with the involvement of A delta myelinated fibers/spinothalamic pathway. The topography of these SEP components was in line with the response of both nociceptive medial and lateral systems, including bilateral M1-S1 and anterior cingu-

late cortical areas. The role of attentive, affective, and (i.e. suppression) motor aspects in the modulation of the SEP components following painful stimulation merits to be investigated in future experiments.

ACKNOWLEDGMENTS

The authors thank Drs. David Niddam, Massimiliano Valeriani, and Domenica Le Pera for their contribution to the achievement of this study. The authors thank also Prof. Fabrizio Eusebi for his continuous support.

REFERENCES

- Allison T, McCarthy C, Wood S, Jones J (1991): Potentials evoked in human and monkey cerebral cortex by stimulation of the median nerve. A review of scalp and intracranial recordings. *Brain* 114: 2465–2503.
- Arendt-Nielsen L (1994): Characteristics, detection, and modulation of laser-evoked vertex potentials. *Acta Anaesthesiol Scand Suppl* 101:7–44.
- Arendt-Nielsen L, Yamasaki H, Nielsen J, Naka D, Kakigi R (1999): Magnetoencephalographic responses to painful impact stimulation. *Brain Res* 839:203–208.
- Babiloni F, Babiloni C, Carducci F, Fattorini L, Onorati P, Urbano A (1996): Spline Laplacian estimate of EEG potentials over a realistic magnetic resonance-constructed scalp surface model. *Electroencephalogr Clin Neurophysiol* 98:363–373.
- Babiloni F, Carducci F, Babiloni C, Urbano A (1998): Improved realistic Laplacian estimate of highly-sampled EEG potentials by regularization techniques. *Electroencephalogr Clin Neurophysiol* 106:336–343.
- Bromm B, Lorenz J (1998): Neurophysiological evaluation of pain. *Electroencephalogr Clin Neurophysiol* 107:227–253.
- Bromm B, Meier W (1984): The intracutaneous stimulus: a new pain model for algesimetric studies. *Methods Find Exp Clin Pharmacol* 6:405–410.
- Becerra LR, Breiter HC, Stojanovic M, Fishman S, Edwards A, Comite AR, Gonzalez RG, Borsook D (1999): Human brain activation under controlled thermal stimulation and habituation to noxious heat: an fMRI study. *Magn Reson Med* 41:1044–1057.
- Birbaumer N, Elbert T, Canavan AG, Rockstroh B (1990): Slow potentials of the cerebral cortex and behavior. *Physiol Rev* 70: 1–41.
- Cakmur R, Towle VL, Mullan JF, Suarez D, Spire JP (1997): Intraoperative localization of sensorimotor cortex by cortical somatosensory evoked potentials: from analysis of waveforms to dipole source modeling. *Acta Neurochir (Vienna)* 139:1117–1124.
- Casey K (1999): Forebrain mechanisms of nociception and pain: analysis through imaging *Proc Natl Acad Sci* 96:7668–7674.
- Chen ACN, Chapman CR (1980): Aspirin analgesia evaluated by event-related potentials in man: possible central action in brain. *Exp Brain Res* 39:359–364.
- Chen ACN (1993): Human brain measures of clinical pain, a review: I. Topographic mappings, *Pain* 54:115–132.
- Chen, ACN, Arendt-Nielsen L, Plaghki L (1998): Laser-evoked potentials in human pain: II. Cerebral generators. *Pain Forum* 7:201–211.
- Chen ACN, Bromm B (1995): Pain-related generators of laser evoked brain potentials: topographic mapping and dipole modeling. In: Bromm B, Desmedt J, editors. *Brain and pain: from nociception to cognition*. New York: Raven Press. p 245–267.
- Coghill RC, Talbot JD, Evans AC, Meyer E, Gjedde A, Bushnell MC, Duncan GH (1994): Distributed processing of pain and vibration by the human brain. *J Neurosci* 14:4095–4108.
- Chudler EH, Dong WK (1983): The assessment of pain by cerebral evoked potentials. *Pain* 16:221–244.
- Daum I, Braun C, Riesch G, Miltner W, Ackermann H, Schugens MM, Birbaumer N (1995): Pain-related cerebral potentials in patients with frontal or parietal lobe lesions. *Neurosci Lett* 197: 137–140.
- Davis KD, Wood ML, Crawley AP, Mikulis DJ (1995): fMRI of human somatosensory and cingulate cortex during painful electrical nerve stimulation. *Neuroreport* 7:321–325.
- Desmedt JE, Huy NT, Bourguet M (1983): The cognitive P40, N60 and P100 components of somatosensory evoked potentials and the earliest electrical signs of sensory processing in man. *Electroencephalogr Clin Neurophysiol* 56:272–282.
- Desmedt JE, Nguyen T, Bourguet M (1987): Bit-mapped color imaging of human evoked potentials with reference to the N20, P22, P27 and N30 somatosensory responses. *Electroencephalogr Clin Neurophysiol* 68:1–19.
- Desmedt JE, Tomberg C (1989): Mapping early somatosensory evoked potentials in selective attention: critical evaluation of control conditions used for titrating by difference the cognitive P30, P40, P100 and N140. *Electroencephalogr Clin Neurophysiol* 74:321–346.
- Devinsky O, Morrell MJ, Vogt BA (1995): Contributions of anterior cingulate cortex to behaviour. *Brain* 118(Pt. 1):279–306.
- Dowman R, Darcey TM (1994): SEP topographies elicited by innocuous and noxious sural nerve stimulation. III. Dipole source localization analysis. *Electroencephalogr Clin Neurophysiol* 92: 373–391.
- Franssen H, Stegeman DF, Wieneke GH (1992): Attenuation of dipoles modeled from SEP due to a lacunar infarct or altered stimulus rate. *Brain Topogr* 5:159–163.
- Frot M, Rambaud L, Guenot M, Mauguiere F (1999): Intracortical recordings of early pain-related CO₂-laser evoked potentials in the human second somatosensory (SII) area. *Clin Neurophysiol* 110:133–145.
- Garcia-Larrea L, Bastuji H, Mauguiere F (1991): Mapping study of somatosensory evoked potentials during selective spatial attention. *Electroencephalogr Clin Neurophysiol* 80:201–214.
- Gevens AS, Cutillo BA, Bressler SL, Morgan NH, White RM, Illes J, Greer DS (1989): Event-related covariances during a bimanual visuomotor task. II. Preparation and feedback. *Electroencephalogr Clin Neurophysiol* 74:147–160.
- Jousmaki V, Forss N (1998): Effects of stimulus intensity on signals from human somatosensory cortices. *Neuroreport* 9:3427–3431.
- Kakigi R (1994): Somatosensory evoked magnetic fields following median nerve stimulation. *Neurosci Res* 20:165–174.
- Kenshalo DR, Willis WD (1991): The role of the cerebral cortex in pain sensation. New York: Plenum Press. p 153–212.
- Kitamura Y, Kakigi R, Hoshiyama M, Koyama S, Shimojo M, Watanabe S (1995): Pain-related somatosensory evoked magnetic fields. *Electroencephalogr Clin Neurophysiol* 95:463–474.
- Kunesch E, Knecht S, Schnitzler A, Tyercha C, Schmitz F, Freund HJ (1995): Somatosensory evoked potentials elicited by intraneural microstimulation of afferent nerve fibers. *J Clin Neurophysiol* 12:476–487.

- Lamour Y, Guilbaud G, Willer JC (1983): Rat somatosensory (Sml) cortex: II. Laminar and columnar organization of noxious and non-noxious inputs. *Exp Brain Res* 49:46–54.
- Lenz FA, Rios M, Zirh A, Chau D, Krauss G, Lesser RP (1998): Painful stimuli evoke potentials recorded over the human anterior cingulate gyrus. *J Neurophysiol* 79:2231–2234.
- Meyer RA, Campbell JN, Raja SN (1994): Peripheral neural mechanisms of nociception. In: Wall PD, Metzack R, editors. *Textbook of pain*. Edinburgh: Churchill Livingstone. p 13–44.
- Melzack R, Casey KL (1968): Sensory, motivational, and central control determinants of pain. A new conceptual model. In: Kenshalo DR, editor. *The skin senses*. Springfield, IL: Charles C. Thomas. p 423–443.
- Miltner W, Braun C, Johnson R Jr, Simpson GV, Ruchkin DS (1994): A test of brain electrical source analysis (BESA): a simulation study. *Electroencephalogr Clin Neurophysiol* 91:295–310.
- Namiki J, Takase M, Ohira T, Goto K, Ishikawa M, Ajimi Y, Toya S (1996): The neural origin generating early cortical components of SEP: topographical analysis using temporal-second-order-differentiation of cortical SEPs. *Brain Topographic* 8:229–232.
- Nunez P (1995): *Neocortical dynamics and human EEG rhythms*. New York: Oxford University Press.
- Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN (1999): Dissociating pain from its anticipation in the human brain. *Science* 284:1979–1981.
- Porro CA, Cettolo V, Francescato MP, Baraldi P (1998): Temporal and intensity coding of pain in human cortex. *J Neurophysiol* 80:3312–3320.
- Posner MI, Walker JA, Friedrich FJ, Rafal RD (1984): Effects of parietal injury on covert orienting of attention. *J Neurosci* 4:1863–1874.
- Posner MI, Petersen SE, Fox PT, Raichle ME (1988): Localization of cognitive operations in the human brain. *Science* 17:1627–1631.
- Posner MI, Dehaene S (1994): *Attentional networks*. *Trends Neurosci* 17:75–79.
- Rainville P, Feine JS, Bushnell MC, Duncan GH (1992): A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. *Somatosens Mot Res* 9:265–277.
- Rossini PM, Babiloni C, Babiloni F, Ambrosini A, Onorati P, Carducci F, Urbano A (1999): “Gating” of human short-latency somatosensory evoked cortical responses during execution of movement. A high resolution electroencephalography study. *Brain Res* 843:161–170.
- Schupp HT, Lutzenberger W, Rau H, Birbaumer N (1994): Positive shifts of event-related potentials: a state of cortical disfacilitation as reflected by the startle reflex probe. *Electroencephalogr Clin Neurophysiol* 90:135–144.
- Sikes RW, Vogt BA (1992): Nociceptive neurons in area 24 of rabbit cingulate cortex. *J Neurophysiol* 68:1720–1732.
- Srisa-an P, Lei L, Tarkka IM (1996): Middle latency somatosensory evoked potentials: noninvasive source analysis. *J Clin Neurophysiol* 13:156–163.
- Steinmetz PN, Roy A, Fitzgerald PJ, Hsiao SS, Johnson KO, Niebur E (2000): Attention modulates synchronized neuronal firing in primate somatosensory cortex. *Nature* 404:187–190.
- Svensson P, Minoshima S, Beydoun A, Morrow TJ, Casey KL (1997): Cerebral processing of acute skin and muscle pain in humans. *J Neurophysiol* 78:450–460.
- Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH (1991): Multiple representations of pain in human cerebral cortex. *Science* 15;251(4999):1355–1358.
- Tarkka IM, Treede RD (1993): Equivalent electrical source analysis of pain-related somatosensory evoked potentials elicited by a CO₂ laser. *J Clin Neurophysiol* 10:513–519.
- Treede RD, Kenshalo DR, Gracely RH, Jones AK (1999): The cortical representation of pain. *Pain* 79:105–111.
- Urbano A, Babiloni F, Babiloni C, Ambrosini A, Onorati P, Rossini PM (1997): Human short latency cortical responses to somatosensory stimulation. A high resolution EEG study. *Neuroreport* 8:3239–3243.
- Woodward SH, Owens J, Thompson LW (1990): Word-to-word variation in ERP component latencies: spoken words. *Brain Lang* 38:488–503.
- Valeriani M, Restuccia D, Di Lazzaro V, Le Pera, D, Barba C, Tonali P, Mauguere F (1998): Dipolar sources of the early scalp somatosensory evoked potentials to upper limb stimulation. Effect of increasing stimulus rates. *Exp Brain Res* 120:306–315.
- Waberski TD, Buchner H, Perkuhn M, Gobbele R, Wagner M, Kucker W, Silny J. 1999. N30 and the effect of explorative finger movements: a model of the contribution of the motor cortex to early somatosensory potentials. *Clin Neurophysiol* 110:1589–1600.
- Wise S, Boussaoud D, Johnson PB, Caminiti R (1997): Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. *Annu Rev Neurosci* 20:25–42.