Cortical Representation of the Human Hand Assessed by Two Levels of High-Resolution EEG Recordings

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Abstract: Increasing interest in cortical plasticity has prompted the growing use of somatosensory evoked potentials (SEPs) to estimate changes in the cortical representation of body regions. Here, we tested the effect of different sites of hand stimulation and of the density of spatial sampling in the quality of estimation of somatosensory sources. Sources of two SEP components from the primary somatosensory cortex (N20/P20 and P45) were estimated using two levels of spatial sampling (64- vs. 128-channel) and stimulation of four distal sites in the upper limbs, including single digits (first vs. fifth) and distal nerves with comparable cortical projection (superficial branch of the radial nerve and distal ulnar nerve). The most robust separation of somatosensory sources was achieved by comparing the cortical representations of the first digit and the distal ulnar nerve territories on the N20/P20 component of SEPs. Although both the 64- and the 128-electrode montages correctly discriminated these two areas, only the 128-electrode montage was able to significantly separate sources in the other cases, notably when using first versus fifth digit stimulation. Trustworthy distinction of cortical representations was not obtainable when using the P45 component, probably because of greater activation volume, radial orientation of sources in areas 1–2 and increased variability with attention and vigilance. Assessment of tangential SEP components to stimulation of first digit versus ulnar nerve appears the best option to assess plastic somatosensory changes, especially when using relatively low-electrode sampling. *Hum Brain Mapp* 32:1894–1904, 2011. © 2011 Wiley Periodicals, Inc.

Key words: somatosensory evoked potentials; N20/P20 potential; P45 potential; source reconstruction analysis; somatotopic representation; EEG spatial sampling

INTRODUCTION

Contract grant sponsors: Région Rhône-Alpes Cluster no. 11 Handicap-Vieillesse-Neurosciences, Fondation pour la Recherche Médicale; Contract grant number: Equipe FRM 2006-2009; Contract grant sponsors: APICIL Foundation for pain relief, the NRJ Foundation, Institut de France.

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Received for publication 20 October 2009; Revised 5 August 2010; Accepted 5 August 2010

DOI: 10.1002/hbm.21155

Published online 18 January 2011 in Wiley Online Library (wileyonlinelibrary.com).

Focal lesions of the somatosensory system can entail profound short-term anatomo-functional changes, both in animals and humans [Bruggemann et al., 2001; Jones and Pons, 1998; Kaas et al., 1999; Rosso et al., 2003], one of these being a modification of cortical somatotopic maps (for reviews, see Jones [2000] and Kaas et al. [2008]). This phenomenon can persist at long-term [Florence and Kaas, 1995], at least in nonhuman primates, leading to a drastic reorganization of the somatosensory cortex (S1). In humans, a number of studies on postamputation pain have also shown that deafferentation creates plastic adaptive changes in the cortical representation of the affected limb and have suggested a close correlation between this

plasticity and the development of phantom limb pain [Flor et al., 2006]. Modification of the cortical somatotopic map described so far was characterized by a spread of the cortical representation of the face, which tends to “invade” that of the amputated limb. In addition, one group of investigators has suggested that the stronger the magnitude of these plastic changes, the stronger the pain will be [Flor et al., 1995]. Therapeutic interventions aiming at reducing pain, such as acupuncture [Napadow et al., 2007], regional anesthesia [Birbaumer et al., 1997], systemic opioids [Huse et al., 2001], or myoelectric prostheses [Lotze et al., 1999], have been reported to induce reorganization of the somatosensory system toward a normalization of previously altered somatotopic maps.

The commonest way used so far to assess cortical somatotopic representation changes, both in healthy subjects and patients, has been dipolar source modeling of somatosensory evoked potentials and fields (SEPs–SEFs) to face and/or upper limb stimulation [Birbaumer et al., 1997; Flor et al., 1995; Grüsser et al., 2001; Karl et al., 2001; Montoya et al., 1998; Rossini et al., 1998; Schaefer et al., 2002a,b; Schwenkreis et al., 2001; Soros et al., 2001; Tecchio et al., 2002; Vartiainen et al., 2009; Waberski et al., 2007]. Although “shrinking” of the upper limb representation, with medial displacement of the face area after amputation is often reported, the correlation between plasticity in S1 and pain remains elusive, a close correlation being observed in a number of studies [Birbaumer et al., 1997; Flor et al., 1995, 1998; Grüsser et al., 2001; Karl et al., 2001; Montoya et al., 1998; Tecchio et al., 2002] but not in others [Schwenkreis et al., 2001; Vartiainen et al., 2009]. Also, while it is often assumed that pain following amputation is the *result* of cortical reorganization, experimental data suggest that pain by itself, without any associated deafferentation, can also induce significant changes in both the amplitude and the cortical distribution of somatosensory responses [Buchner et al., 2000; Flor et al., 1997; Tinazzi et al., 2000].

The vast majority of plasticity studies have been performed using dipole-modeling methods, which heavily rely on the quality of the input data (i.e., the signal to noise ratio) and the spatial sampling (i.e., the number of sensors). These factors have varied widely in the previous literature and might explain some of the differences in conclusions from different studies. A number of studies were performed using “airpuff” stimuli [Flor et al., 1995; Karl et al., 2001; Montoya et al., 1998], which may not yield optimal signal to noise ratios to determine reliably cortical sources. Besides the stimulation mode used, one study was performed with a relatively low-density electrode arrays (32 channels, [Schwenkreis et al., 2001]) while others used more dense arrays with 57–61 electrodes [Birbaumer et al., 1997; Grüsser et al., 2001; Karl et al., 2001; Montoya et al., 1998; Schaefer et al., 2002a]. So far, no one used more than 61 EEG channels. In some cases, digital nerves or mechanical receptors in hands and face were stimulated [Birbaumer et al., 1997; Grüsser et al., 2001;

Karl et al., 2001; Montoya et al., 1998], while others applied nerve trunk stimulation [Buchner et al., 1995; Schwenkreis et al., 2001]. At a first glance, lack of a relationship between spatial shift of somatosensory dipole sources and intensity of neuropathic pain was found in studies using low-spatial sampling (32 EEG electrodes) and nerve trunk stimulation [Schwenkreis et al., 2001], while studies suggesting a relation between cortical plasticity and pain intensity used denser electrode arrays (57–61 electrodes) and digit stimulation [Birbaumer et al., 1997; Grüsser et al., 2001; Karl et al., 2001; Montoya et al., 1998]. However, it should be noted that a recent study using magnetoencephalography (MEG) failed to demonstrate a relation between dipole shift and intensity of neuropathic pain despite a high-spatial sampling (306 sensors) [Vartiainen et al., 2009].

As the interest in cortical plasticity steadily grows, so does the number of studies and the variation of methodologies. It is widely accepted that source localization accuracy and reliability is significantly enhanced when using high-density EEG recordings (>64 electrodes; [Ryynänen et al., 2004]) instead of standard systems of up to 32 channels [Yvert et al., 1997]; also dipole sources to single digit stimulation yield to a sharper cortical somatotopic representation of the hand than this obtained with dipole sources to nerve trunk stimulation.

As part of a larger project aiming at assessing the reorganization of somatosensory maps in neuropathic pain patients, we addressed in this study the three principal variables that may influence the quality of the data when trying to estimate with SEPs the cortical representation of the human hand, namely (a) the spatial sampling (64 vs. 128 electrodes); (b) the peripheral territories stimulated (distal nerve trunks vs. digital nerves), and (c) the cortical response used for estimation (early responses from area 3b vs. later responses from the crown of the postcentral gyrus). Additionally, we compared two modes of graphical illustration of results (on coronal vs. sagittal planes), which may also influence the way results are interpreted.

MATERIALS AND METHODS

Subjects

SEPs recordings were obtained in 10 healthy adult volunteers (4 men, 6 women), 18–61 years old (mean age, 34.2 ± 15.1 years), who gave their informed consent before the study. All but two subjects were right-handed, none had a history of neurological or psychiatric disease, and none of them was under any medication.

SEPs Recordings

Subjects lay on a bed in a quiet, semidarkened room, and were instructed to keep their eyes closed while remaining awake. The left first and fifth digits were

stimulated using ring electrodes (cathode proximal); the ulnar nerve and the superficial branch of the radial nerve were stimulated close to their emergence near the left wrist using a bipolar electrode. The stimuli were square wave pulses of 0.4 ms, delivered at a frequency of 1 Hz and with intensity equal to threefold the sensory threshold. Stimulus intensity was always below the pain threshold for each subject.

SEPs were recorded with a 128-channel EEG cap (Waveguard CapTM) in accordance with the 10–10 extended International System. All electrodes were referred to the left mastoid (M1) ipsilateral to the stimuli, and the ground electrode was incorporated in the cap between AFz and Fz, on the nasion–inion line. The electrode impedance was kept below 5 k Ω . For each stimulated site, two runs of 950 stimuli were applied. Recordings were made using ASA[®] (ANT[®] Software, The Netherlands) at a sampling rate of 2,048 Hz and using a band-pass filter between 0.263 and 1,024 Hz.

SEPs Analyses

SEPs after stimulation of the four sites investigated (first digit, fifth digit, superficial radial nerve, and ulnar nerve) were analyzed within a 15–70-ms latency time window encompassing both the N20/P20 and the P45 SEP components.

In each condition, the continuous EEG was segmented into epochs of 120 ms that included a 20 ms prestimulus period. Before averaging, each epoch underwent correction of slow linear trends by high-pass filtering and baseline correction using the pre-stimulus period. Bandpass filtering was then applied (Butterworth filter, 10–350 Hz, 24 dB/oct) together with a 50-Hz notch filter. A manual artifact rejection was performed. Epochs were visually inspected and rejected from average if voltage variations exceeding ± 70 μ V were present. Under these conditions, 2–16% of epochs were rejected per subject. In two subjects, the SEP signal remained contaminated by low-frequency oscillations after standard bandpass filtering; in these cases, a second high-pass filtering at 20 Hz (24 dB/oct) attenuated low frequencies without altering SEP components in the 15–70 ms range [Mauguière et al., 1995]. Because source localization heavily relies on a good signal-to-noise ratio at all electrode sites, the signal from electrodes that remained of poor quality after the processing steps described earlier (detrending, baseline correction, and filtering) were interpolated using spline functions that took into account the whole set of 128 electrodes. On average, 3 ± 1 electrodes per subject were interpolated. Grand-averages of two consecutive runs for a given stimulation condition were then performed for each subject, before submitting the results to source analysis.

The N20/P20 and P45 SEP components were identified on the basis of their latency, polarity, and scalp distribution, using both the full 128-channel montage and the

smaller 64-channel montage. For each SEP recording and in each subject, the channel in the right parieto-central region exhibiting the largest negative or positive value (around the peak of N20 and P45 SEP, respectively) was identified. Peak latency was estimated at the maximal peak amplitude, and amplitude was measured from the baseline. The channel and values of latency and amplitude of SEPs were then individual-specific.

SEPs Source Reconstructions

Source reconstruction by dipolar modeling was performed using either the whole 128-electrode montage or a standard subset of 64-electrode, both covering evenly the whole scalp. Previous to source analysis, the topographical voltage distribution of the N20/P20 and P45 SEP components was assessed using 3D mapping to ensure that their pattern was in line with the known scalp topography of these components. Dipole source analysis using BESA[®] (MEGIS Software GmbH, Germany) was first based on the grand-average of data obtained in all subjects for each condition. The model obtained for the grand average was then used as a starting point to perform individualized source analysis in each subject and condition. BESA correlates iteratively the scalp potential distributions generated by theoretical dipoles within the brain with the actual scalp distribution obtained experimentally to estimate the location and orientation of intracranial sources best explaining the potentials recorded at the scalp surface. A model with dipole localizations coherent with current anatomical knowledge and a value equal or greater than 90% for the goodness-of-fit (G.O.F.) was accepted as reliable.

The spatial position of each dipole was characterized by their coordinates in a three dimensional referential: the X axis corresponds to the line passing through T7 and T8 (negative values on the left hemisphere), the Y axis to the line between Fpz and Oz (negative values toward the occipital region), and the Z axis to the line perpendicular to the XY plane and passing through Cz (negative values below the head center). The origin of coordinates is defined by the intersection point of the X, Y, and Z axes. The head model used in BESA was an elliptical four-shell of 85-mm radius [Scherg, 1990]. The model used to estimate sources was a nonmoving equivalent current dipole whose magnitude and orientation were allowed to vary across time. The default time window loaded in the BESA source analysis module is 0–120 ms. A relatively long interval fit needs to be chosen to include as much activity as possible but must be sufficiently short to be specific of the activity of interest. In the case of the N20/P20 component, the source localization was performed considering its ascending phase (i.e., 6–10 sampling points). When the subcortical P14 component was in part contained in this time-window, N20 source reconstruction was performed after a brainstem dipole explaining the P14 activity was

Figure 1.

SEPs in response to the four stimulation sites, with scalp maps of N20/P20 and P45 obtained with 64 and 128 electrodes (with M1 as reference). **A:** Overlay of signals recorded at each electrode. Note the smaller N20/P20 amplitude to stimulation of the fifth digit relative to the other stimulation sites. **B, C:** Scalp distribution of the N20/P20 and P45 SEP components to differ-

ent stimulus sites, obtained with 64 (B) and 128 electrodes (C). Whatever the stimulation site, the N20/P20 component showed a dipolar tangential orientation with a phase reversal between frontal and parietal regions following approximately the central sulcus. The P45 component showed a radial orientation with maximal amplitude at centro-parietal electrodes.

identified and fixed. In 30% of cases, a noise dipole accounting for focal EMG noise (neck or periocular EMG) further improved the G.O.F. Then N20 dipole was kept fixed and active during the time window chosen for P45 source localization. When P45 source was active, the N20/P20 dipole had only minimal activity and could be regarded as inactive. P45 dipole modeling was performed on its descending phase during a mean time-period of 6 ms, that is, 12–18 sampling points. After estimation of the best dipolar solution, co-registration of electrode coordinates within the Talairach space allowed projection of the estimated sources onto a Talairach-normalized MRI (MRICro[®] software).

The coordinates of the N20/P20 or P45 dipole in all subjects were averaged to obtain a mean dipole localization and its variance. These coordinates were projected onto a normalized Talairach MRI to specify their anatomical position, and the tri-dimensional (3D) Euclidean distance of

each dipole was calculated with respect to the origin of coordinates in the Talairach system, that is, the anterior commissure. In addition, to assess the interindividual variability between dipole locations, the origin of coordinates was artificially translated to the location of the fifth digit or ulnar nerve dipoles, and the Y–Z coordinates of first digit and radial nerve sources were calculated for each subject relative to this new origin.

Statistical Analyses

After checking the normality of their distributions (Kolmogorov–Smirnov test), data were compared using one-way repeated-measure ANOVA test, followed by post hoc paired *t*-tests. To further ascertain the reproducibility of results, an intersubject comparison was added after dividing our global subject sample in two subgroups of five

TABLE I. Mean and S.E.M. of N20/P20 and P45 latencies (ms) and amplitudes (V) obtained with 64- and 128-electrode montages for each stimulation site

		1st Digit		5th Digit		Radial Nerve		Ulnar Nerve	
		Latency	Amplitude	Latency	Amplitude	Latency	Amplitude	Latency	Amplitude
N20/P20 (128)	mean $\pm$ s.e.m.	21.8 $\pm$ 0.58	−0.88 $\pm$ 0.10	21.45 $\pm$ 0.49	−1.07 $\pm$ 0.10	18.95 $\pm$ 0.49	−1.37 $\pm$ 0.22	19.55 $\pm$ 0.46	−1.59 $\pm$ 0.27
N20/P20 (64)	mean $\pm$ s.e.m.	21.45 $\pm$ 0.53	−1.17 $\pm$ 0.08	21.65 $\pm$ 0.61	−0.80 $\pm$ 0.11	18.7 $\pm$ 0.56	−1.35 $\pm$ 0.21	19.75 $\pm$ 0.44	−1.53 $\pm$ 0.27
P45 (128)	mean $\pm$ s.e.m.	44.11 $\pm$ 1.33	1.52 $\pm$ 0.25	44.05 $\pm$ 1.17	1.50 $\pm$ 0.28	43.55 $\pm$ 0.70	1.96 $\pm$ 0.35	42.55 $\pm$ 0.91	1.84 $\pm$ 0.28
P45 (64)	mean $\pm$ s.e.m.	41.72 $\pm$ 1.28	1.37 $\pm$ 0.19	43.25 $\pm$ 1.00	1.31 $\pm$ 0.25	44.25 $\pm$ 0.62	2.45 $\pm$ 0.28	42.3 $\pm$ 1.04	1.80 $\pm$ 0.34

Each mean value was obtained by averaging values recorded in each subject at the level of the electrode exhibiting the largest SEP amplitude.

subjects each. For all tests used, the level for statistically significant difference was set at $P < 0.05$, after Tukey's correction for post-hocs.

RESULTS

The N20/P20 SEP Component: Topographic Distribution and Source Dipolar Modeling

Whatever the stimulation site and the number of electrodes used, a dipolar voltage distribution (posterior negative and anterior positive) over the hemisphere contralateral to stimulation was recorded in all subjects at about 20-ms poststimulus (N20/P20), with the isoelectric line grossly overlapping the central region (Fig. 1B and 1C corresponding to data obtained with the 64- and 128-electrode montages, respectively). Mean values and standard errors of the mean (s.e.m.) of N20/P20 latencies and amplitudes are given in Table I.

When compared with digit stimulation, the N20/P20 component elicited by the stimulation of radial and ulnar nerves occurred at significantly shorter latencies both with the 128- (repeated measures ANOVA, $P < 0.0001$, post hoc paired t -test, $P < 0.0001$) or 64- (repeated measures ANOVA, $P < 0.0001$, post hoc paired t -test, $P < 0.0001$) electrode montage.

The electrodes exhibiting the largest N20/P20 amplitude were identified in each of the 40 SEP recordings obtained. In 72% of the cases, the largest amplitude of the N20/P20 component was observed on electrodes belonging specifically to the 128-electrode montage.

The Talairach coordinates of N20/P20 equivalent dipoles for each stimulation site and spatial sampling are summarized in Table II. Figure 2A shows the projection of each N20/P20 averaged dipoles obtained with the 128-electrodes montage onto a Talairach-normalized MRI. Figure 3 shows source localizations in one representative subject, superimposed on his own MRI, which follows the pattern of the whole group. When using the highest spatial sampling (128 electrodes), the 3D Euclidean distances of SEP sources corresponding to the four stimulation sites were significantly different [repeated measures ANOVA, $F(3,27) = 6.117$, $P = 0.002$]. Post hoc paired t -test specified that 3D distances significantly differed between the first versus fifth digit dipoles [$t(9) = 3.14$, $P = 0.012$], first digit versus ulnar nerve dipoles [$t(9) = 2.49$, $P = 0.034$], and fifth digit versus radial nerve dipoles [$t(9) = 2.55$, $P = 0.031$]. With 64-electrodes, although the overall differences in 3D Euclidean distances of the four SEP sources were also significant [repeated measures ANOVA: $F(3,27) = 3.168$, $P = 0.04$], the level of significance was much lower than when using a higher spatial sampling and on post hoc paired t -tests only the 3D Euclidean distances of first digit and ulnar nerve dipoles were found significantly different [$t(9) = 2.778$, $P = 0.021$].

TABLE II. Mean and S.E.M. of Talairach coordinates (mm) and G.O.F. (%) of N20/P20 and P45 dipoles obtained with 64 and 128 electrodes

	1st Digit						5th Digit						Radial Nerve						Ulnar Nerve					
	x			y			x			y			x			y			x			y		
	mean	s.e.m.	G.O.F.	mean	s.e.m.	G.O.F.	mean	s.e.m.	G.O.F.	mean	s.e.m.	G.O.F.	mean	s.e.m.	G.O.F.	mean	s.e.m.	G.O.F.	mean	s.e.m.	G.O.F.	mean	s.e.m.	G.O.F.
N20/P20 (128)	38.85 ± 2.37	3.25	89.70 ± 0.66	-17.56 ± 3.25	1.96	36.34 ± 1.96	38.75 ± 1.60	-24.92 ± 3.89	46.03 ± 2.31	90.61 ± 0.47	40.78 ± 1.96	-21.7 ± 3.85	41.16 ± 1.56	90.50 ± 0.64	35.06 ± 1.92	-21.9 ± 3.59	45.52 ± 2.38	90.68 ± 0.64						
N20/P20 (64)	42.07 ± 1.45	3.80	92.12 ± 0.44	-17.86 ± 3.80	2.22	35.83 ± 2.22	34 ± 3.09	-22.97 ± 4.19	46.04 ± 3.10	93.07 ± 0.91	37.17 ± 1.34	-20.82 ± 3.18	44.13 ± 1.91	93.41 ± 0.51	35.14 ± 2.63	-22.17 ± 3.22	46.84 ± 2.46	91.97 ± 0.65						
P45 (128)	38.11 ± 1.27	4.71	90.22 ± 1.41	-17.63 ± 4.71	1.75	45.6 ± 1.75	38.88 ± 2.78	-14.89 ± 2.90	45.3 ± 2.59	93.91 ± 0.62	38.25 ± 1.53	-18.68 ± 4.17	44.13 ± 2.71	92.20 ± 0.74	34.81 ± 1.72	-26.38 ± 4.62	40.05 ± 1.58	91.47 ± 1.10						
P45 (64)	35.12 ± 2.40	4.87	92.43 ± 0.92	-18.76 ± 4.87	1.86	41.11 ± 1.86	36.6 ± 1.77	-17.19 ± 3.12	42.31 ± 2.89	94.34 ± 0.48	38.27 ± 1.70	-15.99 ± 4.23	44.23 ± 2.33	93.35 ± 0.69	35.00 ± 2.14	-24.25 ± 4.24	37.89 ± 3.16	92.76 ± 1.12

Figure 2.

Projection of N20/P20 and P45 averaged dipoles obtained with the 128-electrode montage onto a Talairach-normalized MRI. Dipoles representing digit versus digit, digit versus nerve and nerve versus nerve conditions were projected on a sagittal plane ($X = 44$) of a Talairach-normalized MRI. The size of the ellipsoidal forms and bars indicate the 95% confidence interval for source localizations. **A:** Projection of N20/P20 averaged dipoles, **B:** Projection of P45 averaged dipoles. For the N20/P20 SEP, the four source localizations were significantly different, except those from the two nerves condition (radial nerve vs. ulnar nerve) which overlapped. For the P45 SEP, no comparison was significantly different.

Intersubject comparison between the two subgroups of five subjects issued from the whole 10 subjects sample yielded no significant differences in source localization, whatever the spatial sampling.

Figure 4 shows the projection of each N20 averaged dipole obtained with the 128- and 64-electrode montage onto a Talairach-normalized MRI. The Y–Z coordinates of the first digit and the radial nerve dipoles obtained with the 128-channel montage, relative to the ulnar nerve

and fifth digit sources are illustrated for each subject in Figure 5.

The P45 SEP Component: Topographic Distribution and Source Dipolar Modeling

Whatever the stimulation site and EEG montage, a central positive field contralateral to the stimulation was recorded at 40–45-ms poststimulus (P45) for all simulation sites in 9 of the 10 subjects (Fig. 1B,C corresponding to data obtained with the 64- and 128-electrode montages, respectively). The remaining subject did not show any field distribution consistent with a P45 after first digit stimulation. Mean data $\pm$ s.e.m. for P45 latency and amplitude are given in Table I. Peak latencies of P45 to different stimulation sites did not vary significantly whatever the spatial sampling.

The electrodes exhibiting the largest P45 amplitude were identified in each of the 40 SEP recordings obtained. In 33% of the cases, the largest amplitude of the P45 component was observed on electrodes belonging exclusively to the 128-electrode montage.

Individual P45 source reconstruction could be obtained when the fifth digit, the radial or the ulnar nerve was stimulated in all subjects and whatever the spatial sampling montage. Conversely, the P45 equivalent dipole after first digit stimulation could not be modeled in two subjects with a GOF superior to 90%. Table II shows means $\pm$ s.e.m. of the 3D Euclidean distances of P45 dipoles for each stimulation site obtained with the 64- and 128-electrode montages. Figure 2B shows the projection of each P45 averaged dipole obtained with the 128-electrode montage onto a Talairach-normalized MRI. Whatever the electrode sampling, the differences between the 3D Euclidean distances of P45 sources corresponding to the four stimulation sites did not reach statistical significance, and inter-subject *t*-tests showed no difference between the two subgroups.

DISCUSSION

Stimulus Site, Spatial Sampling, and Mode of Source Comparison

In the majority of studies devoted to S1 somatotopic changes, investigators compared source locations of SEPs obtained by stimulating the first and fifth digits of the hand and recorded with a maximal number of 61 EEG channels [Birbaumer et al., 1997; Grüsser et al., 2001; Karl et al., 2001; Montoya, 1998; Schaefer et al., 2002b]. To evaluate the reliability and reproducibility of this approach, we used two levels of EEG electrode sampling (64- and 128-electrode) to compare the localization of S1 SEP sources to stimulation of these same digits. Furthermore, we extended our investigation to SEPs obtained after stimulation of superficial radial and ulnar nerves, which have a

Figure 3.

Superimposition of N20/P20 source localizations obtained with the 128-electrode montage in one subject on his own MRI. Dipoles corresponding to the four stimulated territories of the hand are located in SI area and organized according to Penfield's homunculus.

Figure 4.

Projection of N20/P20 averaged dipoles obtained with the 128- and the 64-electrode montage. All dipoles are located in SI area of the standard MRI. Dipoles obtained with the 128-electrode montage are organized according to Penfield's homunculus. With the 64-electrode montage, the fifth digit, ulnar, and radial nerves dipoles are clustered, and only the 3D Euclidean distances of ulnar nerve and first digit dipoles are significantly different.

Figure 5.

Relative position of N20/P20 radial nerve and first digit dipole sources in each subject with respect to the localization of fifth digit (left column) and ulnar nerve source localization (right column), using the 128 electrodes montage. The individual positions of first digit sources are best clustered and correctly situated in anterior–inferior position relative to the ulnar nerve

sources when compared with position relative to fifth digit sources. Whatever the reference site, individual radial nerve dipolar positions are the most spread out. Coordinates with an asterisk (*) refer to individual localizations that were obviously wrong (e.g., radial nerve dipoles placed more posterior than fifth digit or ulnar nerve sources).

cortical representation that overlaps that of the first and fifth digits, respectively.

SEP source localization using the maximal spatial sampling (128 electrodes) allowed discriminating significantly the 3D localization of all of the digit–digit or digit–nerve combinations tested. The cortical organization of the hand estimated from the N20/P20 sources was in line with Penfield’s homunculus [Penfield and Boldrey, 1937], the average localization of radial nerve, and first digit dipoles being anterior and inferior to that of the fifth digit and ulnar nerves (Figs. 2A and 4). As expected from physiological considerations, comparing the localization of single digits or of nerve trunks versus digits yielded 3D Euclidean distances larger than comparing nerve trunks between them. No significant difference in location was obtained between the cortical projection of cutaneous territories and their corresponding nerve trunks.

Degrading the spatial sampling from 128 to 64 electrodes entailed the “loss” of several recording points yielding maximal SEP amplitudes (see also van de Wassenberg et al. [2009]), and this resulted in a poorer quality of cortical source separation. Thus, with the smaller montage the “classical” first to fifth digit contrast showed significant spatial overlap at the group level, and only the combination of first digit versus ulnar nerve still yielded a significant 3D separation of cortical sources. The statistical power, although not very high with 10 subjects, was enough to demonstrate significant interdigit and inter-nerve source localization differences using 128 electrodes—and not 64. This implies that, for an identical statistical power, source separation was less robust using 64 than 128 electrodes and that peripheral sites allowing the easiest source separation are to be privileged if only 64 sensors are used.

Anatomically, sound head models, exact registration of sensor location, and accurate conductivity estimates—particularly of skull conductivity—should improve still further the quality of source localization in the following years. Skull resistivity is the main factor in EEG smearing on the scalp surface, which limits the intrinsic spatial resolution of the EEG. Recent reports suggest, however, that the skull may be less resistive than previously estimated [Oostendorp et al., 2000], and these estimates may allow higher spatial frequency of the human EEG than previously believed. Should this be confirmed, greater spatial sampling than offered by 128-channel arrays should further improve the quality and accuracy of cortical representation estimates, and some reports have suggested that interelectrode distances of 1 cm—or about 500 channels—may be required to fully represent the spatial frequency of the scalp EEG [Freeman et al., 2003, Ryyänänen et al., 2006].

SEPs to stimulation of the fifth digit commonly have small amplitude and a weak signal-to-noise ratio, making source localization difficult [Baumgartner et al., 1993; Buchner et al., 1995]. Using 32 and 48 electrodes, Baumgartner et al. [1993] reported that the dipole localization of the fifth digit was hardly reproducible across subjects and showed substantial overlap with others digits. Using MEG, Hari et al. [1993] also showed that the dipole strength of fifth digit was the weakest of all digits. In this study, and whatever the spatial sampling, both G.O.F. and signal-to-noise ratios obtained after fifth digit stimulation were smaller than those obtained for the first digit. Furthermore, stimulating the ulnar nerve instead of the fifth digit provided a gain in amplitude of 48–90% on the N20/P20 SEP using the 64- and 128-channel montages, respectively, and a gain of 22–37% on P45 SEP. This superiority of nerve versus digit stimulation was not observed in the

outer aspect of the hand, where stimulation of the first digit yielded responses of equal or superior quality to those obtained after radial nerve stimulation, and with less intersubject variability than the latter. Therefore, our results do support the use of first digit stimulation, but lend very moderate support to the use of fifth digit stimulation for source modeling purposes, unless a very dense spatial sampling can be ensured. Further to spatial sampling, appropriate modeling of SEPs to the fifth digit requires a number of stimuli higher than those used in most studies dealing with plastic SEPs changes. Unless optimal conditions of sampling and signal-to-noise ratios are met, ulnar nerve SEPs can replace advantageously fifth digit SEPs for localization purposes.

Plastic changes in somatosensory cortical sources have been so far very commonly assessed on the basis of the inferior–superior location of dipoles (i.e., localization changes within the Z-axis). This was quantified either as changes in the Z-coordinates of the dipolar sources, changes in the θ angle (elevation) from the center of the brain volume to the estimated source, measured on the X–Z plane (coronal slices; [Birbaumer et al., 1997]) or as the mean shift in the coronal plane [Flor et al., 1995]. Single-subject analysis in the present study suggests, however, that the coronal projections are clearly suboptimal to quantify changes in cortical somatic representation within the primary sensory-motor cortex, because they miss information relative to the anterior–posterior position of dipoles. Indeed, the axis of the central sulcus being oblique, the cortical representation of the fifth digit is more posterior than that of the first digit, itself more posterior than that of the face. Calculations based on coronal projections do not take into account the antero-posterior location of dipoles and may therefore miss important changes in source localization. Sagittal projections, on the contrary, adequately reflect changes in both the Z and the Y-axes. In our study, single-subject analysis of cortical sources on the sagittal plane confirms the large interindividual variance of S1 somatotopy (Fig. 5; [Hari et al., 1993]). It also indicates that radial nerve sources were often poorly estimated, as they were found posterior, rather than anterior to the ulnar or fifth digit sources in five and three cases, respectively (asterisk * on Fig. 5). This indicates that radial nerve stimulation was a poorer option than first digit stimulation—a fact that would have passed unnoticed if a coronal projection had been chosen instead of a sagittal one. We suggest that the representation of plastic changes in somatotopy using SEPs should be presented either on 3D volumes or, at least, on sagittal planes.

Spatial Discrimination Based on N20/P20 or P45 SEP Components

Not surprisingly, source localization of the N20/P20 component proved more stable and reproducible across subjects than that of the middle-latency P45. There are sev-

eral theoretical reasons that make the P45 a less-suited component for somatotopic SEP studies. First, the P45 reflects activation of a larger neuronal population than the N20, as indicated by its higher amplitude and larger scalp distribution, two factors, which may contribute to a less robust dipole localization for the P45. Since its early description, the scalp distribution of the P45 was shown to be more diffuse and variable than that of the N20 [Desmedt and Bourguet, 1985]. The concentric scalp distribution of P45 (see Fig. 1) suggests a radial orientation of its neural generators in the crown of the central gyrus, and intracranial recordings indeed documented its origin in somatosensory area 1 [Allison et al., 1992]. Dipolar reconstruction of radial neural generators is commonly more difficult and imprecise than that of tangential sources like those of N20/P20, and, for instance, somatosensory sources radial to the scalp did not exhibit a somatotopic arrangement while tangential sources did [Buchner et al., 1995]. The small number of electrodes below the canthomeatal line may be one technical reason contributing to this, as it prevents to correctly model the “queue” of the dipolar field. On physiological grounds, the primates’ areas 1 and 2 in the crown of the postcentral gyrus receive not only direct thalamic input, but also projections from other somatosensory areas [Krubitzer and Kaas, 1990], thus making receptive fields larger than those of 3b area. Accordingly, Overduin and Servos [2004] showed, using 4-Tesla fMRI, that although both areas 3b and 1 had somatotopic arrangements of digits, the representations of area 1 were larger and had lesser interdigit scaling than those observed in the area 3b. All these factors make radial sources such as those of the P45 component less-adapted for the assessment of cortical somatotopic changes in S1.

Contrary to the N20/P20, the P45 is significantly influenced by the subject’s attentional and vigilance state. Thus, P45 amplitude increases significantly when attention is actively directed to the stimulated hand [Desmedt et al., 1983; Josiassen et al., 1982], whereas drowsiness and sleep have depressing effects on P45 amplitude [Noguchi et al., 1995] leading to amplitude decreases down to levels near background noise. This might explain why P45 was virtually non identifiable in two of our subjects who became drowsy during the recordings. Conversely, the N20/P20 component is neither affected by the attentional state [Garcia-Larrea et al., 1991] nor by the vigilance state of the subject with the exception of a slight shift in latency in sleep stages II, III, and IV [Yamada et al., 1988].

To conclude, the SEP N20/P20 component obtained by stimulating the first digit and ulnar nerve using a 128-electrode montage appears as the best approach to evaluate potential plastic reorganization of the cortical somatotopic representation.

REFERENCES

- Allison T, McCarthy G, Wood CC (1992): The relationship between human long-latency somatosensory evoked potentials

- recorded from the cortical surface and from the scalp. *Electroencephalogr Clin Neurophysiol* 84:301–314.
- Baumgartner C, Doppelbauer A, Sutherling WW, Lindinger G, Levesque MF, Aull S, Zeitlhofer J, Deecke L (1993): Somatotopy of human hand somatosensory cortex as studied in scalp EEG. *Electroencephalogr Clin Neurophysiol* 88:271–279.
- Birbaumer N, Lutzenberger W, Montoya P, Larbig W, Unertl K, Topfner S, Grodd W, Taub E, Flor H (1997): Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. *J Neurosci* 17:5503–5508.
- Bruggemann J, Galhardo V, Apkarian AV (2001): Immediate reorganization of the rat somatosensory thalamus after partial ligation of sciatic nerve. *J Pain* 2:220–228.
- Buchner H, Adams L, Muller A, Ludwig I, Knepper A, Thron A, Niemann K, Scherg M (1995): Somatotopy of human hand somatosensory cortex revealed by dipole source analysis of early somatosensory evoked potentials and 3D-NMR tomography. *Electroencephalogr Clin Neurophysiol* 96:121–134.
- Buchner H, Richrath P, Grunholz J, Noppeney U, Waberski TD, Gobbels R, Willmes K, Treede RD (2000): Differential effects of pain and spatial attention on digit representation in the human primary somatosensory cortex. *Neuroreport* 11:1289–1293.
- Desmedt JE, Bourguet M (1985): Color imaging of parietal and frontal somatosensory potential fields evoked by stimulation of median or posterior tibial nerve in man. *Electroencephalogr Clin Neurophysiol* 62:1–17.
- 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.
- Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E (1995): Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature* 375:482–484.
- Flor H, Braun C, Elbert T, Birbaumer N (1997): Extensive reorganization of primary somatosensory cortex in chronic back pain patients. *Neurosci Lett* 224:5–8.
- Flor H, Elbert T, Muhlcnickel W, Pantev C, Wienbruch C, Taub E (1998): Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. *Exp Brain Res* 119:205–212.
- Flor H, Nikolajsen L, Staehelin Jensen T (2006): Phantom limb pain: A case of maladaptive CNS plasticity? *Nat Rev Neurosci* 7:873–881.
- Florence SL, Kaas JH (1995): Large-scale reorganization at multiple levels of the somatosensory pathway follows therapeutic amputation of the hand in monkeys. *J Neurosci* 15:8083–8095.
- Freeman WJ, Holmes MD, Burke BC, Vanhatalo S (2003): Spatial spectra of scalp EEG and EMG from awake humans. *Clin Neurophysiol* 114:1053–1068.
- Garcia-Larrea L, Bastuji H, Mauguire F (1991): Mapping study of somatosensory evoked potentials during selective spatial attention. *Electroencephalogr Clin Neurophysiol* 80:201–214.
- Grüsser SM, Winter C, Muhlcnickel W, Denke C, Karl A, Villringer K, Flor H (2001): The relationship of perceptual phenomena and cortical reorganization in upper extremity amputees. *Neuroscience* 102:263–272.
- Hari R, Karhu J, Hamalainen M, Knuutila J, Salonen O, Sams M, Vilkmann V (1993): Functional organization of the human first and second somatosensory cortices: A neuromagnetic study. *Eur J Neurosci* 5:724–734.
- Huse E, Larbig W, Flor H, Birbaumer N (2001): The effect of opioids on phantom limb pain and cortical reorganization. *Pain* 90:47–55.
- Jones EG (2000): Cortical and subcortical contributions to activity-dependent plasticity in primate somatosensory cortex. *Annu Rev Neurosci* 23:1–37.
- Jones EG, Pons TP (1998): Thalamic and brainstem contributions to large-scale plasticity of primate somatosensory cortex. *Science* 282:1121–1125.
- Josiassen RC, Shagass C, Roemer RA, Ercegovac DV, Straumanis JJ (1982): Somatosensory evoked potential changes with a selective attention task. *Psychophysiology* 19:146–159.
- Kaas JH, Florence SL, Jain N (1999): Subcortical contributions to massive cortical reorganizations. *Neuron* 22:657–60.
- Kaas JH, Qi HX, Burish MJ, Gharbawie OA, Onifer SM, Massey JM (2008): Cortical and subcortical plasticity in the brains of humans, primates, and rats after damage to sensory afferents in the dorsal columns of the spinal cord. *Exp Neurol* 209:407–416.
- Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H (2001): Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. *J Neurosci* 21:3609–3618.
- Krubitzer LA, Kaas JH (1990): The organization and connections of somatosensory cortex in marmosets. *J Neurosci* 10:952–974.
- Lotze M, Grodd W, Birbaumer N, Erb M, Huse E, Flor H (1999): Does use of a myoelectric prosthesis prevent cortical reorganization and phantom limb pain? *Nat Neurosci* 2:501–502.
- Mauguière F, Garcia-Larrea L, Murray NMF, Rogers T (1995): Evoked potential diagnostic strategies. In: Osselson JW, Binnie CD, Cooper R, Fowler CJ, Mauguire F, Prior P, editors. *Clinical Neurophysiology*. London: Butterworths. pp350–481.
- Montoya P, Ritter K, Huse E, Larbig W, Braun C, Topfner S, Lutzenberger W, Grodd W, Flor H, Birbaumer N (1998): The cortical somatotopic map and phantom phenomena in subjects with congenital limb atrophy and traumatic amputees with phantom limb pain. *Eur J Neurosci* 10:1095–1102.
- Napadow V, Liu J, Li M, Kettner N, Ryan A, Kwong KK, Hui KK, Audette JF (2007): Somatosensory cortical plasticity in carpal tunnel syndrome treated by acupuncture. *Hum Brain Mapp* 28:159–171.
- Noguchi Y, Yamada T, Yeh M, Matsubara M, Kokubun Y, Kawada J, Shiraishi G, Kajimoto S (1995): Dissociated changes of frontal and parietal somatosensory evoked potentials in sleep. *Neurology* 45:154–160.
- Oostendorp TF, Delbeke J, Stegeman DF (2000): The conductivity of the human skull: Results of in vivo and in vitro measurements. *IEEE Trans Biomed Eng* 47:1487–1492.
- Overduin SA, Servos P (2004): Distributed digit somatotopy in primary somatosensory cortex. *Neuroimage* 23:462–472.
- Penfield W, Boldrey E (1937): Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 60:389–443.
- Rossini PM, Tecchio F, Pizzella V, Lupoi D, Cassetta E, Pasqualetti P, Romani GL, Orlacchio A (1998): On the reorganization of sensory hand areas after mono-hemispheric lesion: A functional (MEG)/anatomical (MRI) integrative study. *Brain Res* 782:153–166.
- Rosso T, Aglioti SM, Zanette G, Ischia S, Finco G, Farina S, Fiaschi A, Tinazzi M (2003): Functional plasticity in the human primary somatosensory cortex following acute lesion of the anterior lateral spinal cord: Neurophysiological evidence of short-term cross-modal plasticity. *Pain* 101:117–127.

- Ryynänen OR, Hyttinen JA, Laarne PH, Malmivuo JA (2004): Effect of electrode density and measurement noise on the spatial resolution of cortical potential distribution. *IEEE Trans Biomed Eng* 51:1547–1554.
- Ryynänen OR, Hyttinen JA, Malmivuo JA (2006): Effect of measurement noise and electrode density on the spatial resolution of cortical potential distribution with different resistivity values for the skull. *IEEE Trans Biomed Eng* 53:1851–1858.
- Schaefer M, Muhlnickel W, Grüsser SM, Flor H (2002a): Reliability and validity of neuroelectric source imaging in primary somatosensory cortex of human upper limb amputees. *Brain Topogr* 15:95–106.
- Schaefer M, Muhlnickel W, Grüsser SM, Flor H (2002b): Reproducibility and stability of neuroelectric source imaging in primary somatosensory cortex. *Brain Topogr* 14:179–189.
- Scherg M (1990): Fundamentals of dipole source potential analysis. Auditory evoked magnetic fields and electric potentials. In: Grandori F, Hoke M, Romani GL, editors. *Advances in Audiology*. Basel: Karger.
- Schwenkreis P, Witscher K, Janssen F, Pleger B, Dertwinkel R, Zenz M, Malin JP, Tegenthoff M (2001): Assessment of reorganization in the sensorimotor cortex after upper limb amputation. *Clin Neurophysiol* 112:627–635.
- Soros P, Knecht S, Bantel C, Imai T, Wusten R, Pantev C, Lutkenhoner B, Burkle H, Henningsen H (2001): Functional reorganization of the human primary somatosensory cortex after acute pain demonstrated by magnetoencephalography. *Neurosci Lett* 298:195–198.
- Tecchio F, Padua L, Aprile I, Rossini PM (2002): Carpal tunnel syndrome modifies sensory hand cortical somatotopy: A MEG study. *Hum Brain Mapp* 17:28–36.
- Tinazzi M, Fiaschi A, Rosso T, Faccioli F, Grosslercher J, Aglioti SM (2000): Neuroplastic changes related to pain occur at multiple levels of the human somatosensory system: A somatosensory-evoked potentials study in patients with cervical radicular pain. *J Neurosci* 20:9277–9283.
- van de Wassenberg WJ, van der Hoeven JH, Leenders KL, Maurits NM (2009): 128-Channel somatosensory evoked potentials in the differential diagnosis of Parkinsonian disorders. *Parkinsonism Relat Disord* 15:564–571.
- Vartiainen N, Kirveskari E, Kallio-Laine K, Kalso E, Forss N (2009): Cortical reorganization in primary somatosensory cortex in patients with unilateral chronic pain. *J Pain* 10:854–859.
- Waberski TD, Dieckhofer A, Reminghorst U, Buchner H, Gobbele R (2007): Short-term cortical reorganization by deafferentation of the contralateral sensory cortex. *Neuroreport* 18:1199–1203.
- Yamada T, Kameyama S, Fuchigami Y, Nakazumi Y, Dickins QS, Kimura J (1988): Changes of short latency somatosensory evoked potential in sleep. *Electroencephalogr Clin Neurophysiol* 70:126–136.
- Yvert B, Bertrand O, Thevenet M, Echallier JF, Pernier J (1997): A systematic evaluation of the spherical model accuracy in EEG dipole localization. *Electroencephalogr Clin Neurophysiol* 102:452–459.