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Whole-head MEG analysis of cortical spatial organization from unilateral stimulation of median nerve in both hands: No complete hemispheric homology

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We examined the contralateral hemispheric cortical activity in MEG (151 ch) after unilateral median nerve stimulation of the right and left hand in twenty healthy right-handed subjects. The goal was to establish parameters to describe cortical activity of the hemispheric responses and to study the potential ability to assess differences in volunteers and patients. We focused on the within-subject similarity and differences between evoked fields in both hands. Cortical activity was characterized by the overlay display of waveforms (CWP), number of peak stages, loci of focal maxima and minima in each stage, 3D topographic maps and exemplified equivalent current dipole characteristics. The paired-wise test was used to analyze the hemispheric differences. The waveform morphology was unique across the subjects, similar CWPs were noted in both hemispheres of the individual. The contralateral hemispheric responses showed a well defined temporal–spatial activation of six to seven stages in the 500 ms window. Consistently (in over 80% of subjects), the six stages across the subjects were 20M, 30M, 50M, 70M, 90M, and 150M. A 240M was present in the left hemisphere (LH) in 15/20 subjects and in the right hemisphere (RH) in 10/20. Statistics of the latencies and amplitudes of these seven stages were calculated. Our results indicated that the latency was highly consistent and exhibited no statistical mean difference for all stages. Furthermore, no mean amplitude differences between both hemispheres at each stage were found. The patterns of magnetic fields in both hemispheres were consistent in 70% of the subjects. A laterality index (L.I.) was used for defining the magnetic field amplitude differences between two hemispheres for each individual. Overall, the absolute amplitude of the brain responses was larger in the left than in the right hemisphere in the majority of subjects (16/20), yet a significant portion (4/20) exhibited right dominance of the N20m activity. Each individual exhibited a unique CWP, there was reliable consistency of peak latencies and mean amplitudes in median nerve MEG. Nevertheless, this study indicates the limitations of using the intact hemisphere responses to compare with those from the affected (brain) side and suggests caution in assuming full homology in the cortical organization of both hemispheres. This study provides some results to address clinical issues like which parameter describes individual differences best. Whether a genuine difference is found or whether any difference may simply represent the variability encountered in a normal population.

Keywords: Median nerve stimulation; Magnetoencephalography; Evoked fields; Interhemispheric comparison; Magnetic flux; Functional mapping

Introduction

In the past 30 years of magnetoencephalography (MEG) research, the hardware technology changed from a single sensor to over 300 SQUID sensors and the software from simple signal detection to complex MEG/MRI co-registration with various types of source analyses. This advance has greatly improved our appreciation of the brain organization in health and its reorganization after disease conditions (Rossini et al., 2001). MEG is reputed with special sensitivity to generators that reside in the sulcus and gyrus of the cortex, favoring a tangential orientation of the equivalent dipole representing 80% of the human brain sources (Flemming et al., 2001). It is almost independent of the electrical resistance distribution in the head and does not need a reference. Thus, MEG is suitable to localize brain activities in spite of its difficulty to detect both radial generators and deep sources. One major field of MEG studies is focused on somatosensory research from healthy subjects to patients afflicted with a diversity of diseases

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and traumas. A better understanding of how cortical plasticity in brain reorganization is related to the use (e.g. training effects) or disuse (e.g. deafferentation or stroke) and practical applications of MEG for clinical diagnosis/prognosis of disease sequelae can be anticipated. In MEG source imaging of clinical applications, caution is being discussed in recent publications (Babiloni et al., 2004; Fuchs et al., 2004; Rossini and Dal Forno, 2004). Particularly, the use of MEG in tracing the source (Wheless et al., 2004) is drawing a significant debate (Barkley and Baumgartner, 2003; Baumgartner, 2004; Lesser, 2004; Parra et al., 2004).

The first MEG report on somatosensory evoked fields, SEFs (Baumgartner et al., 1991), demonstrated the anterior–parietal pattern of N20m–P20m and the reversal of the P30m–N30m in the contralateral hemisphere in response to median nerve stimulation in one hand. Rossini et al. (1994) compared the hemispheric differences of the evoked fields to unilateral hand stimulation of both hands, and the homology implications were reported in a study on phantom limb pain (Karl et al., 2001; Schaefer et al., 2002). Rossini et al. (1994) focused on the location and strength of the equivalent sources activated in the primary somatosensory cortex (<50 ms) contralateral to the stimulated nerve. The equivalent current dipole (ECD) model was used with the main aim of making a quantitative comparison between the responses of the two hemispheres. The spatial coordinates of the equivalent sources did not differ statistically significantly in the two hemispheres, but the strengths (in nA) of the equivalent sources were significantly higher in the left hemisphere. This contralateral effect was confirmed in a small group of subjects (Soros et al., 1999).

A “normative” data set was established in another Italian sample (Tecchio et al., 1998, 2000) using the interhemispheric correlation coefficient as a parameter to study physiological and pathological neural connectivity. It was noted that consistency of SEFs across a hemisphere within a subject is far greater than among subjects. In the wave morphology, the similarity across the hemisphere is well defined as an individual signature between subjects. Wikström et al. (1997) studied the primary sensorimotor (SM1) and secondary somatosensory (SII) activation. The conclusion was that at the individual level the median nerve SEFs from the contralateral primary sensorimotor cortex (SMI) could be used to detect abnormally large interhemispheric asymmetries. The window of analysis has extended beyond the early stages to mid-latency somatosensory activation, from <50 ms to >100 ms. Kakigi (1994) demonstrated that the deflections, N90m–P90m, were generated in the contralateral second sensory cortex (SII), a small N90m–P90m was identified in the hemisphere ipsilateral to the stimulation site. It is emphasized that the lack of responses in the sensory association cortices (parietal areas) may be due to radial-oriented dipoles. The majority of the studies use equivalent current dipole (ECD) modeling to examine the sources of M20 and M30 in the SEFs. It is important to note that various assumptions are inherently imbedded in different methods of dipole analysis. For example, the N20m–P20m and P30m–N30m have often been explored with a single moving dipole model as a generator residing at the posterior bank of 3b for M20 (Kanno et al., 2003). In contrast, the generator of the M30 remains undetermined in case it is modeled by a single generator (Hari et al., 1993; Kakigi, 1994; Wikström et al., 1997; Hoshiyama and Kakigi, 2001), however, the measurements can be explained by assuming two generators (Kawamura et al., 1997) in the SI–MI area. When dealing with mid-latency and late stages of SEP/SEF, the spatio-temporal dynamics become even more complicated than at short latency stages. We question whether source localization and related parameters are the only way for the study of pathological conditions. In this study, therefore, we examined the normal state of cortical activities (evoked magnetic fields) in both hemispheres in response to standard median nerve stimulation in a window of 450 ms. We aimed at identifying the major parameters that practically could be used in a descriptive and analytical way for future clinical studies of neurological dysfunction and disease in patients. These studied parameters are important and based on the quantified hemispherical differences of the measured data. The parameters of the study deemed to be compact and easy to use in a clinical context. Finally, we aimed at comparing the differential effects between the right and left hemisphere (RH and LH) in response to contralateral hand stimulation under identical stimulation conditions.

Materials and methods

Subjects and median nerve stimulation

Twenty volunteers (14 males and 6 females, age range 32–45 years, all right handed) were recruited from the hospital staff, adequately informed, and gave their consent. The Medical Ethical Committee of the Free University Hospital approved of this study. All subjects were healthy without neurological dysfunction. Handedness was established both using lists from the VU Medical Center which included arm and leg performance, secondary the Edinburgh Inventory which produced a lowest value of 0.8 (7/20 subjects). Median nerve stimulation was performed at the wrist with a bipolar electrode, the cathode proximal (IFCN Guideline: Nuwer et al., 1994). Electrical stimulation was used since it is a very precise and common way of stimulation, and it can induce the early components. To stimulate the median nerve in a standard way, we employed an electrical stimulator (Grass, USA; model S48) using a photoelectric stimulus isolation unit (Grass, USA; model SIU7). The stimulation current was pulsed, at a repetition rate of 2 Hz and with a pulse duration of 0.2 ms. All subjects were studied in one session, lasting about 45 min. Stimulation was in counter-balanced order between right and left hand across the subjects. Between stimulation of both hands, a resting period of 5–10 min was ensured. Stimulus intensity was tailored to the individual twitching level of each separate hand and reached a 1.5× motor twitching level. The twitch threshold varied with the subject, was well tolerated, and painless. Typical values were 6.1–7.7 mA (±1.1 mA). Five hundred events were recorded from the wrist surface of the median nerve in each hand.

MEG recordings

MEG measurement data were recorded using a 151-channel whole-head VSM gradiometer system (VSM MedTech Ltd., Canada) in a 3-layer magnetically shielded room (Vacuum Schmeltze Gmbh, Germany). The layout of the recording montage and coordinate system is illustrated in Fig. 1.

The x, y, and z coordinate system is based upon the nasion, left and right ear (pre-auricular points), the location where the coils are positioned that are used to determine the distance between the head and the measurement system. Using the positions of these fiducials, a head centered coordinate frame is defined. The positions of all MEG sensors in head coordinates are thus known.

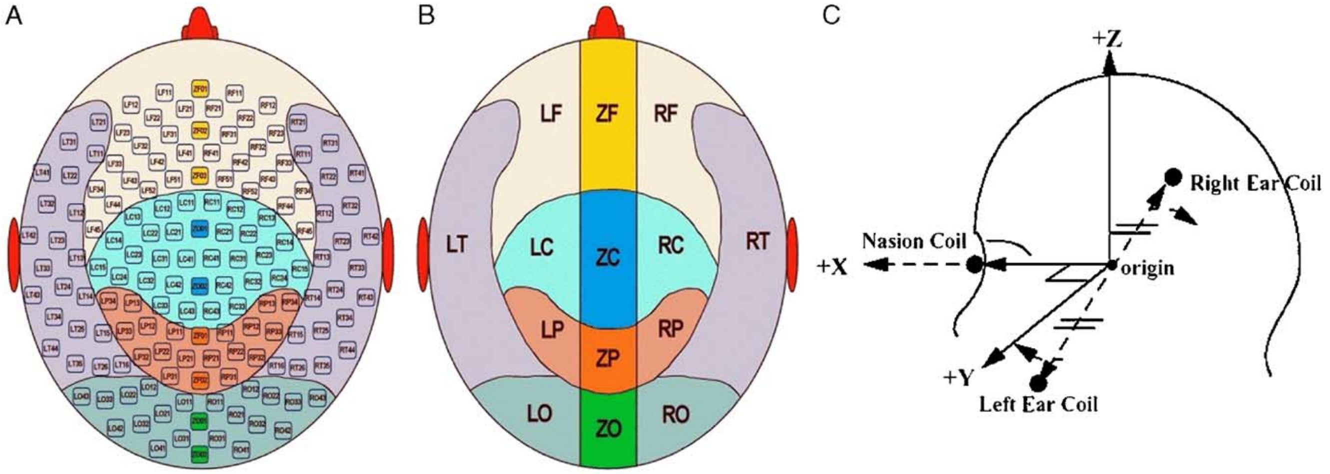

Fig. 1. (A–C) In the left panel (A), montage of the 151 sensors is displayed and in the middle panel (B) the spatial relations. In the right panel (C), the x, y, and z coordinate system of the VSM MEG. Left (L) and Right (R) are the hemispherical sides, Z is for the midline, F (frontal), C (central), T (temporal), P (parietal), and O (occipital) depict the sensor groups related to different cortical areas. With permission: VSM MedTech Ltd. (Canada).

Using the coordinates of the sensors in multiple recording sessions, corresponding to multiple head positions, we determined the best recording position, as the position in which the smallest rotation and translations were necessary to align all data sets. We determined the amount of rotation and translation needed to fit the actual recording position to that best recording position by averaging the absolute values of the rotation angles and the norms of the translation vectors (i.e. the distances) This was done for all recordings in each subject, leading to a measure of the reproducibility of head positioning per subject and, for all recording, leading to a description of the reproducibility of the head position of subjects and the variations in head size. For the recordings per subject, the positional variations were quite small; the mean rotation angle amplitude was 3.8°, the mean translation distance was 4 mm. For the recordings of the entire group, the variations were larger, the mean rotation angle amplitude was 5.6°, the mean translation distance was 8 mm. The average subjects head was positioned 0.2 mm left from the center of the helmet. Recordings were performed in synthetic 3rd-order gradient mode, using the manufacturer's real-time software (Vrba and Robinson, 2001). All subjects were in a comfortable supine position with the head well positioned in the helmet without much space left to move which might alter the position. The MEG signals were sampled at 1250 Hz, triggered on the synchronization pulse of the electric stimulator. The peri-stimulus interval was 50 ms pre-trigger and 450 ms post-trigger. On-line filters were set at DC for high-pass and at 400 Hz (4th order Butterworth) for anti-aliasing low-pass. No on-line or off-line high pass filters were used that might influence the outcome of the data, only a correction for DC based on the pre-stimulus interval of 50 ms. The system has a baseline of 5 cm. Off-line, the MEG data were screened for artifacts, averaged, and DC-corrected using the pre-trigger interval to determine the recording offset. Furthermore, +/− averages were calculated to obtain noise-level estimates. The estimated distance between two neighboring sensors in the area of our interest is 2.67 cm.

MRI recordings

Of all 20 subjects, an MRI was made with a 3D-1.5T (Siemens Sonata) MRI using the same measuring protocol in two hospitals. The protocol was as follows: slice orientation was sagittal, thickness 2 mm, TR11.8 ms, number of echoes 1, TE 5 ms, flip angle 30°, number of signals averaged 2, scan matrix 256, and reduction matrix 256. The results presented in Table 3 are based upon twenty individual MRIs.

Compressed waveform profile (CWP)

When the responses of all sensors are superimposed, a butterfly-like overlay plot is produced. We termed this whole-head overlay plot the compressed waveform profile (CWP) from which the peak activation stages were isolated. It is conventional to define the somatosensory activities in the time domain into three different phases, an early (<50 ms), mid-latency (50–90 ms), and late (90–400 ms) phase, each containing peak stages. The compressed waveform profile can effectively provide characteristics of the brain dynamics of the sensory, motor, and perceptual brain regions. Moreover, it can exhibit individual patterns for the different subjects.

Focal extrema

At each peak stage, the extrema reflect the sites of magnetic efflux and influx, respectively. From the topographic SEF pattern, the magnetic gradients and the locus of underlying current dipole can be deduced. The amplitudes of the focal extrema were used for statistical analyses.

Laterality index (L.I.)

A conventional index of the differences and the level of lateralization between the left hemisphere (LH) and right hemisphere (RH) responses is computed as the laterality index (L.I.) (Jung et al., 2003) according to the formula:

$$\mathrm{L.I.} = (\mathrm{LH} - \mathrm{RH})/(\mathrm{LH} + \mathrm{RH})$$

where (LH − RH) in this study is the difference in amplitudes between the LH and the RH response at the focal extrema (efflux and influx) expressed in femtotesla (fT) (see also Fig. 5). This means that in each hemisphere at a given peak latency two values are computed, the efflux (red) having a positive value and the influx (blue) as a negative one. All N20 (blue bars) depict the indices of the LH and RH based upon the influxes, all P20 (red bars) represent the effluxes. We focused on two latencies, 20 and 30 ms, since these two early peak latencies are well studied. When both hemispheres are equal in SEF magnitude of a subject, the L.I. on the *y* axis should be zero. Thus, a positive L.I. indicates a higher magnitude in left (dominant) hemisphere than in the right one. If the L.I. is negative (down), there is less activation in LH than in the (dominant) RH.

Equivalent current dipole and dipole parameters

VSM (CTF) software was used to obtain the equivalent current dipoles (ECD) describing the MEG data collected with the VSM-whole-cortex MEG/EEG system (151 sensors) and based upon the coordinate system depicted in Fig. 1C. The head was approximated with a spherical volume conductor for source analysis of MEG data. A conventional single equivalent current (moving) dipole analysis (e.g. Lin and Kajola, 2003; Fuchs et al., 2004) was used in this study for data evaluation. MEG data were co-registered with MR images using fiducial coils and vitamin E markers. The head model was chosen to match the inner contour of the skull. This matching was done by eye. Epochs in the post-stimulus 450 ms time window, with clear SEF deflections (as judged by comparison of average and plus minus average signal amplitudes), were visually identified to select the cortical areas of interest for further analysis. At each of the peak stages, the dipole characteristics were determined, data are only presented of the M20 and M30.

Data management and statistical analysis

First stage data analysis was done during measurements using the VSM software (release v4.16). The analysis window was 50 ms before and 450 ms after the stimulation. Each subject was asked to relax, to ignore the stimuli as much as possible, and to keep the eyes open and refrain from blinking during the recording. A small number (max 50) of events containing too much disturbances due to movement or blinking were rejected for each data set manually. All further data analysis and presentation were performed employing software from ASA (Advanced Source Analysis, ANT A/S, The Netherlands) for graphical display.

Only the contralateral activity was analyzed in this study for comparison of the hemispheric activation in response to both right and left hand stimulation. In the first step, we created the compressed waveform profile (CWP) of all 151 channels of SEFs in each subject and identified the (peak) stages. In our study, we employed the following parameters: the latency and the number of the (peak) stages, site of activity (*x*, *y*, and *z*), focal activity (magnitude), and the patterns of activation (3D—topographic maps). In order to compare the two hemispheres, we derived the following parameters: latency differences, laterality indices, and the coefficient of variation (cv), an index of measurement consistency. All these parameters could be extracted without retort to dipole analyses. We finally studied overlay plots and grand averages of all subjects and established the dipole localizations of the M20 and M30 peak stages in relation to an individual MRI. A series of statistical analysis were conducted to compare these parameters in the hemispheres from right vs. left hand stimulation of the median nerve. Paired *t* test was employed to evaluate the studied effects, with alpha of 0.05 adopted as significant.

Results

Compressed waveform profile (CWP) in SEFs

Fig. 2 depicts the morphology of the CWP between the right (RHc) and left hemispherical (LHc) cortex in response to contralateral median nerve stimulation and contrast of CWPs in each hemisphere among twenty subjects.

The left panel (RHc) displays the contralateral activation in response to left median nerve stimulation, while the right panel shows the contralateral hemispherical (LHc) activation to right median nerve stimulation. The maximum amplitude (vertically presented) was between 300–400 fT, and the time window presented was restricted in all CWPs to 350 ms (horizontal axis). CG is the code for the volunteers, the results of 10 are depicted. Inspection of Fig. 2 demonstrates large inter-subjects variability in CWPs, a relatively high intra-individual consistency of the two CWPs however in response to contralateral activation of both hands. It is noted that each subject revealed his/her unique signature. In all subjects, both sharp early peaks can be distinguished as stages of high activity at later latencies, which extended over many milliseconds (i.e. CG01 and CG04).

In our subjects, up to 6–7 stages could be identified (see Table 1). The initial one was an M20 and M30 stage in all subjects followed by the M50 stage in the left (18/20 subjects) and right (17/20 subjects) hemisphere. The largest energy is found in the mid-latency M70 (all 20 subjects) and at the later stage M90 (both sides 18/20 subjects). The first two peaks (M20/M30) are quite sharp, but the fourth peak (around 70 ms, see Table 2), apart from its high amplitude, may extend over 50–80 ms in duration, see Fig. 2 subject CG-04. At 150M, another peak can be identified (left 18/20 and right 20/20 subjects) as a 240M (left 15/20 and right 10/20, respectively). Identification of the peaks at these stages was not only based upon the morphology alone but also upon maximum root mean square (RMS) values. The RMS value is calculated over a data range that is selected from the overlay traces (CWPs) of all artifact-free channels that are displayed and is an indication of power. We can identify appreciable differences in both morphology and (peak) stages between RH and LH in each subject. Thus, for detailed analysis of brain measures, it is more accurate to examine the individual profile than to describe the averaged event-related SEF as is often reported in the literature. Statistical analysis indicates no difference in the number of stages between the two stimulated hands (Table 1). However, when comparing the two hemisphere peak activations, some values (in bold-italic) were not homologous, though there was a large agreement.

Overlay plot vs. grand averaged compressed waveform profiles

To appreciate the similarity and differences of the CWPs across the subjects, an overlay display was created which can be compared to the CWP of the grand average of the group. Fig. 3 illustrates the differences in CWP between two displays showing larger and more differentiated signals in the overlay plot than in the grand average.

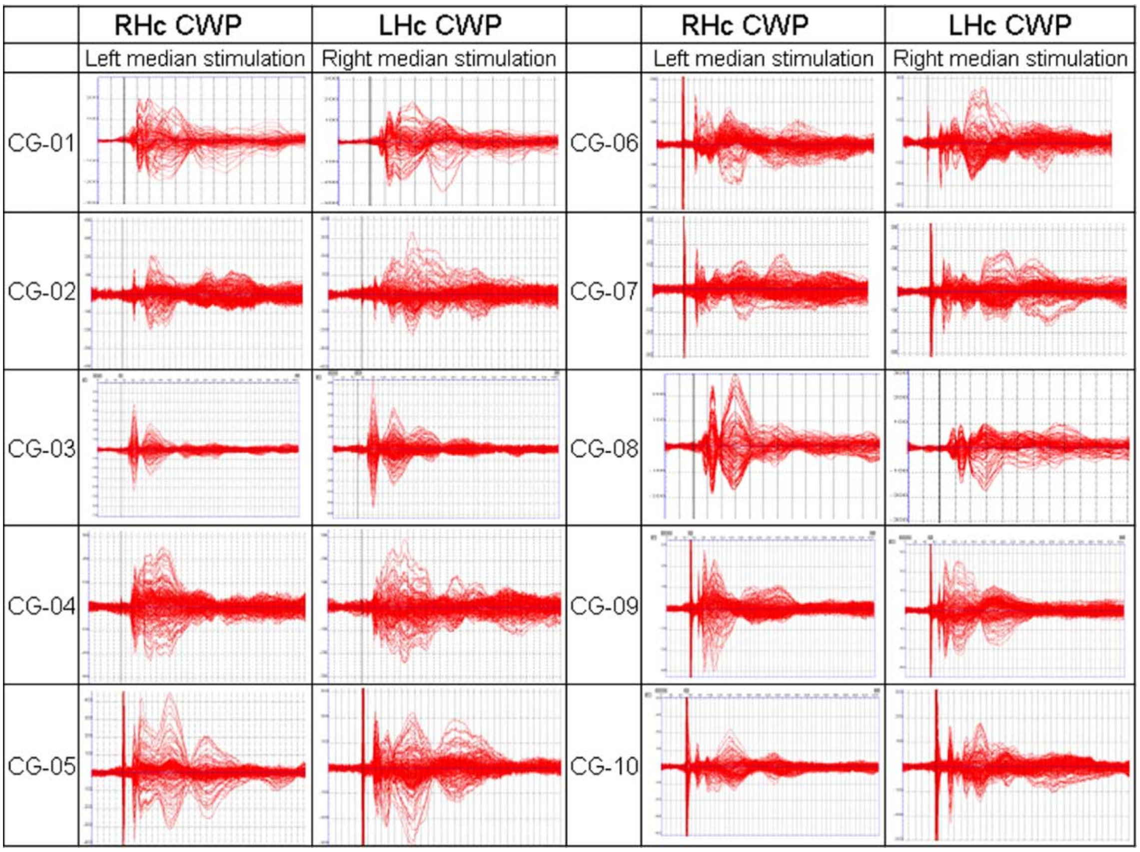

Fig. 2. Compressed waveform profiles (CWP), the superimposed channel waves for the 151 sensors in the 20 normal healthy subjects. The magnetic field strength (amplitude in fT) is vertical, and the time window (0–350 ms) is horizontal. Most CWPs have an amplitude range from −350 to 350 fT, where necessary another scale was used, i.e. CG-05 where the range was from −50 to 500 fT. CG-01 and CG-08 are based upon a time window of 1 s during measurements and produced a different horizontal scaling.

3D topography of somatosensory evoked fields

At three peak latencies, 20, 30, and 70 ms, the 3D topography of SEFs is displayed to illuminate the spatio-temporal dynamics of the cortical evoked magnetic field. These cortical dynamics are shown in Fig. 4 for a typical subject (CG-09).

In the upper part of Fig. 4 (CH), the evoked fields on the contralateral cortex after median nerve stimulation are shown. A clear dipolar configuration is found at these three latencies, the polarities in the RHc and LHc are in general opposite. The well known polarity reversal between 20 and 30 ms is clearly seen, as is the stability of the polarity and magnetic field localization until 90 ms (also see Fig. 5). In the lower part of Fig. 4, in the ipsilateral hemisphere (IH), cortical activity is shown at the same latencies. Cortical responses on the ipsilateral side display activity that is not simply dipolar. These responses are initially more temporoparietal but from 30 ms on more frontally localized. To appreciate the full range of brain activity, the results of one subject are presented in detail. In Fig. 5, the isofield contour maps of a typical volunteer (CG-09) are depicted at different latencies. The field distribution shows a dipolar configuration from the fast first peak at 20 ms until 250 ms. This is true for both hemispheres at comparable peak maxima at around 20, 30, 50, 70, 90, 150, and 240 ms.

Across the time window of 0–350 ms, 7 sequential activations are observed as a bipolar pair at 20, 30, 50, 70, 90, 150, and 240 ms. Between 20 and 30 ms, the evoked field polarity begins to invert, and this is seen in both hemispheres. This first polarity reversal is seen in 17/20 subjects. In 3/20 subjects, however, two early peak latencies are seen in the period of 20–24 ms. In these three subjects, the polarity reversal was observed already between these to early peaks. In two subjects, the reversal occurred later, between 40 and 52 ms, in one subject in both hemispheres, in two subjects only in the LH or RH. In the LHc, the evoked field remains stable up to around 90 ms where the amplitude decreases, and at around 150 ms, the field is inverted again, and a second polarity reversal is observed, again

Table 1
Peak activation stages observed for all 20 subjects in both hemispheres

Median left hemisphere (LHc)							Median right hemisphere (RHc)						
20 ms	30 ms	40 ms	70 ms	90 ms	150 ms	240 ms	20 ms	30 ms	40 ms	70 ms	90 ms	150 ms	240 ms
20/20	**20/20**	18/20	**20/20**	18/20	18/20	15/20	**20/20**	**20/20**	17/20	**20/20**	18/20	20/20	10/20

At different latencies, different number of (peak) stages were found.

Table 2
Parameter values of the hemispheric responses to the unilateral median nerve stimulation (the bold-italic values are the major differences between the two hemispheres)

Latencies (ms)	M20	M30	M50	M70	M90	M150	M240
Stages	1	2	3	4	5	6	7
Right hemisphere (mean)	20.9	32.8	44.2	68.6	92.0	148.5	252.5
(Standard deviation—SD)	1.8	2.4	4.9	6.4	9.0	18.3	30.5
cv (SD/mean)	0.08	0.07	0.11	0.09	0.09	0.10	0.12
LH (mean)	21.0	32.1	48.4	73.3	93.2	150.8	235.5
(SD)	1.9	2.3	4.3	5.4	8.6	22.1	15.9
cv	0.09	0.07	0.08	0.07	0.09	0.12	0.06
Latency diff. (absolute)	0.1	0.7	4.2	***4.7***	1.2	2.3	***17.0***
Efflux in MEF (fT)							
RH (mean)	140.0	198.0	154.7	214.9	169.5	116.4	68.1
(SD)	87.5	105.3	84.3	82.8	56.2	50.6	19.5
cv	0.62	0.53	0.54	0.38	0.33	0.43	0.3
LH (mean)	174.6	210.8	166.8	220.8	168.5	122.5	68.8
(SD)	81.8	120.3	101.0	92.3	100.3	60.9	42.4
cv	0.50	0.57	0.60	0.41	0.59	0.49	0.6
Ratio RH/LH	0.8	0.93	0.92	0.97	1.0	0.95	1.0
Amplitude diff.	***34.6***	***12.8***	***12.1***	5.9	1.0	6.1	0.7
Influx in MET (fT)							
RH (mean)	−168.9	−204.4	−150.4	190.6	−151.5	−112.6	−62.9
(SD)	69.1	122.6	91.5	77.3	66.7	55.1	31.0
cv	−0.40	−0.6	0.6	0.40	0.4	0.5	0.5
LH (mean)	−173.7	−206.9	−155.7	−200.7	−176.3	−107.3	−67.4
(SD)	99.0	107.6	92.6	67.7	76.5	74.6	24.8
cv	0.6	0.5	0.59	0.33	0.43	0.69	0.4
Ratio RH/LH	1.0	1.0	0.96	0.9	0.9	1.04	0.9
Amplitude diff.	4.8	2.5	5.3	***10.1***	***24.8***	5.3	4.5

cv = coefficient of variation.

cortical activity is dipolar but not as clear. In the RHc, similar evolution can be seen. The corresponding SEF waveforms at each maximum and minimum site are illustrated in Fig. 5. The second polarity reversal is seen in 17/20 subjects, in 2 subjects, no reversal at all is seen, and in 1 subject only over the left hemisphere.

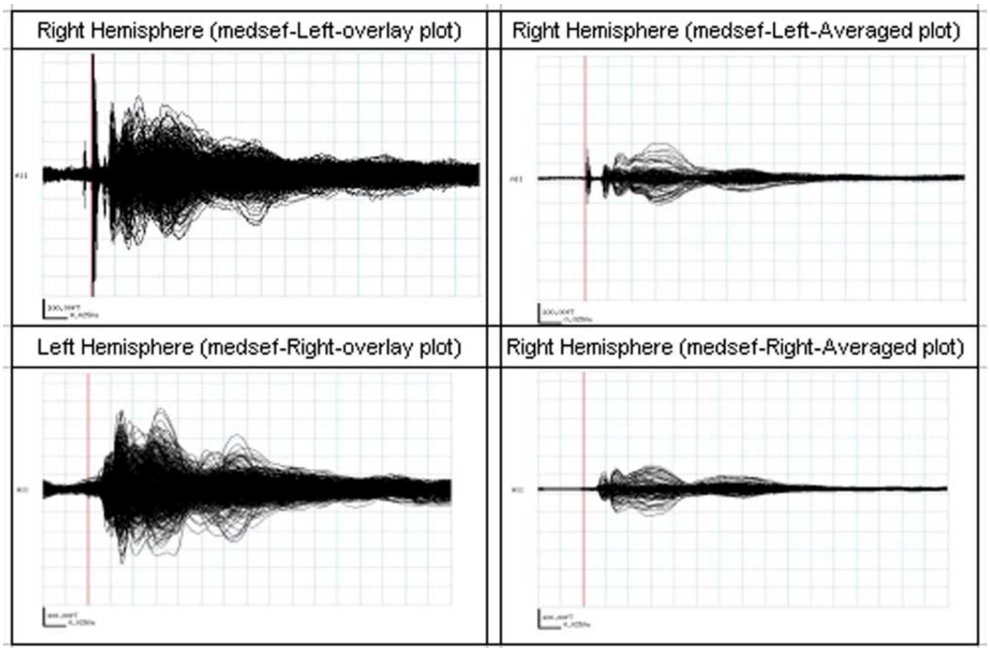

Fig. 3. The left part of the figure presents the overlay plot of the CWPs of 20 healthy volunteers after left and right electrical median nerve stimulation. The right part depicts the averaged CWPs of the same group. The enclosed scales: 100 fT in magnitude bar, 250 ms in time bar.

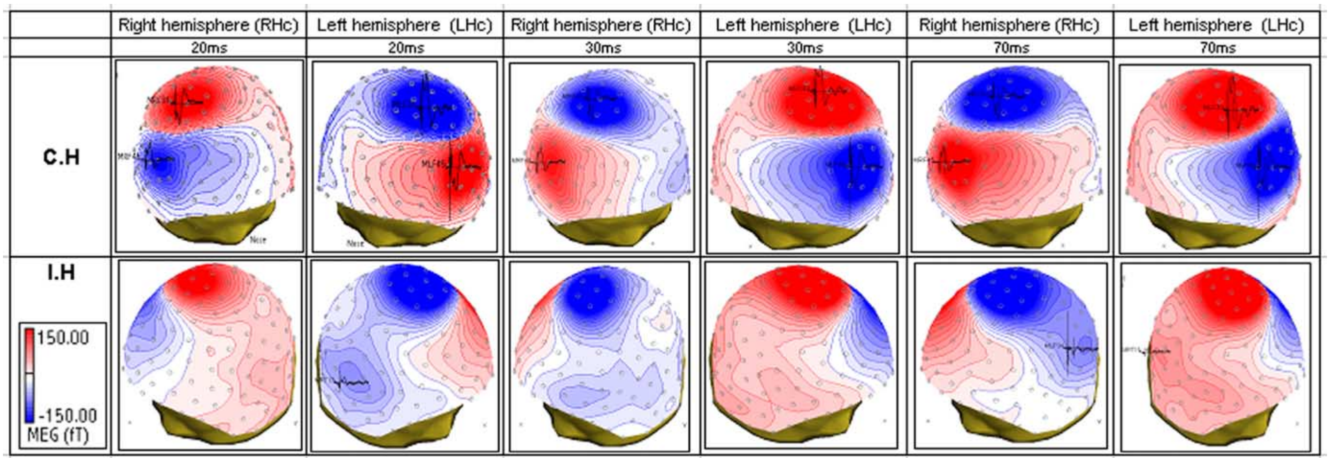

Fig. 4. Comparison of the patterns observed in the contralateral (C.H.) and the ipsilateral hemisphere (I.H.) in response to a left and right median nerve stimulation, in one single subject at 20 ms, 30 ms, and 70 ms.

SEF maxima and minima, peak latencies, and amplitudes

Table 2 provides an overview of the 7 peaks; their averaged latencies, the standard deviations over both hemispheres, the absolute latency, and amplitude differences. From these data, it follows that there are no statistically discernible differences between the two hemispheres. The dispersion of variability across subjects is noticeable (cv), especially in the later stages. Large interhemispheric variations within each activation stage are found. These values (in bold-italic) in Table 2 clearly illustrate substantial differences between two hemispheres at the latencies of M70 (mean of 4.7 ms) and M240 (mean of 17.0 ms), as well as differences larger than 10 fT in some amplitudes.

However, in the left hemisphere, the values of the positive amplitudes are shown in the majority of subjects. These results clearly indicated that there was no complete hemispheric homology in brain activation magnitudes, even though the mean values in each stage were consistently larger compared with those in the right hemisphere.

Laterality index of hemispheric activities

The laterality index (L.I.), i.e. (LH − RH) / (LH + RH), is used to express the proportion of the “left-hemispheric dominance” and is only based on the amplitudes of the focal maxima and minima. Fig. 6 clearly demonstrates a majority of subjects having left-hemispheric dominance based upon amplitude, although some subjects, i.e. 4/20 in N20 and 5/20 in N30, have a right-hemispheric dominance. The N20 and P20 showed distinctive patterns. The L.I. of N20 and N30 in the group are not the same, though both exhibited left hemisphere predominance (positive L.I.). In some subjects, a 50% higher amplitude in one hemisphere was found over the other. Such results would be considered “pathological” (Jung et al., 2003). These results clearly indicate that there is no complete hemispheric homology in brain activation magnitudes even in our healthy subjects.

Dipole parameters and hemispheric differences

Table 3 lists the mean of the parameters of the equivalent dipoles at the time instants of M20 and M30 of all 20 subjects using a single moving dipole model. The confidence intervals (C.I.) for all parameters are listed. The 95% C.I. is defined as

$$\mathrm{CI} = \mathrm{mean} \pm 1.96 \times \mathrm{SE}$$

and the standard error (SE) as $\mathrm{SE} = \mathrm{SD} / \sqrt{n}$, where n is the number of subjects in the group, and SD is the standard

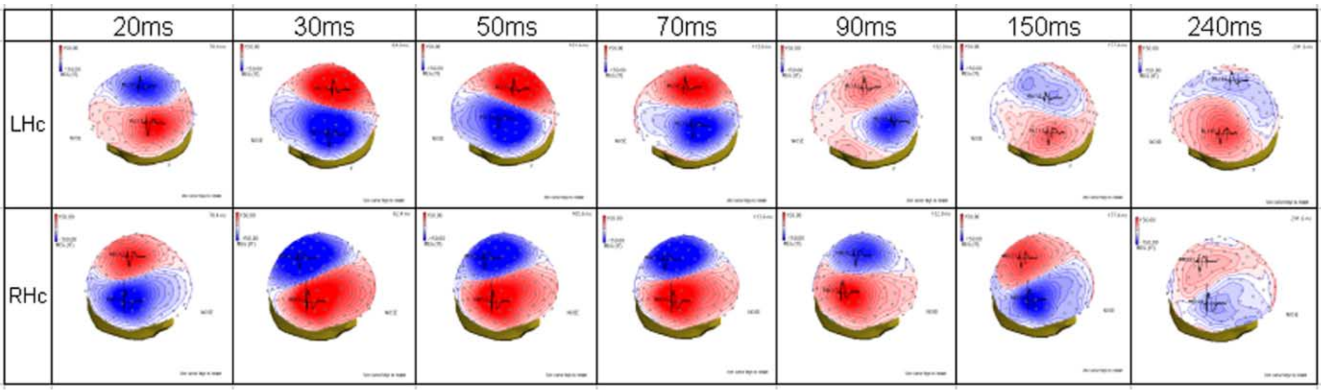

Fig. 5. The hemispheric spatial pattern of the evoked fields to median nerve stimulation for the contralateral left hemisphere (LHc) to the right hand stimulation and the contralateral right hemisphere (RHc) to the left hand stimulation in a single representative subject (HCG-09). In the top bar, the different latencies are depicted, from M20 to M240. Efflux is depicted in red, influx in blue. Polarity reversal is both observed between 20/30 ms and 90/150 ms. A new observation of polarity reversal of the evoked field at 90/150 ms is also shown in both hemispheres.

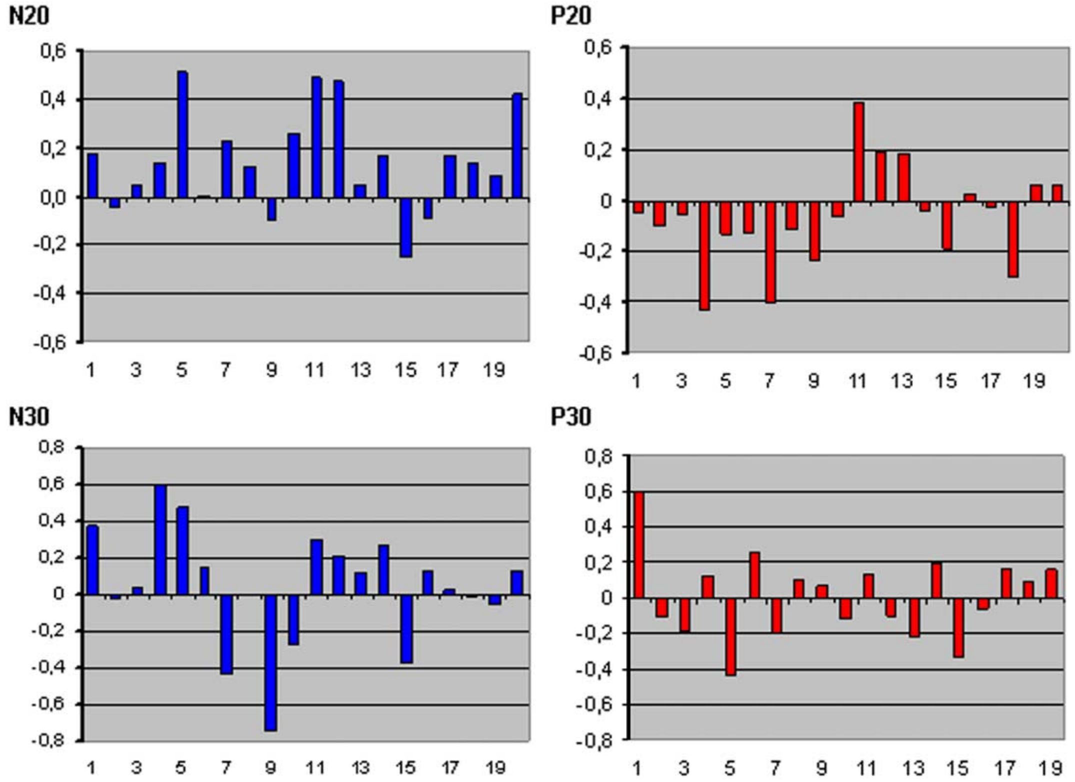

Fig. 6. This figure demonstrates the distribution of the laterality index of 20 healthy subjects. Laterality index of the early cortical activation is defined as the (L.I. = <LH − RH> / <LH + RH>) at the early M20 and M30 peak stages. Scales: amplitudes in fT in the vertical magnitude bar, numbers in horizontal bar.

deviation. Few of these parameters showed significant difference of means between the left and right hemisphere to contralateral median nerve stimulation. Though no group difference was shown statistically, there remained an appreciable absolute difference between two hemispheres within each subject when the values are examined on their individual basis (shown in Table 3).

Correlations of field magnitudes and dipole moments between two hemispheres

At the early phase (M20–M50), the SEF influx and efflux were significantly correlated between two hemispheres, but not at the middle phase (M70, M90). At the late stage, only the activities at M150 of both hemispheres were correlated (see Table 4A). No

Table 3
The dipole parameters in the right and left hemispheres in response to unilateral median nerve stimulation at 20M and 30M

Peaks	Nerve	$N = 20$		Position (cm)			Orientation in degrees		Strength
				x	y	z	Declination	Azimuth	nA
20 ms	L. median	20/20	mean	0.83	−3.56	8.7	76.7	19.9	23.19
			SD	0.93	1.71	0.6	13.8	12	8.29
			cv (SD/mean)	1.12	0.47	0.06	0.17	0.6	0.35
			95% C.I.	−7.9 to 9.49	−18.7 to 11.5	3.37 to 14.3	46.1 to 199.5	−86.7 to 126.5	−50.6 to 97
	R. Median	20/20	Mean	0.40	4.30	8.6	78.2	307.6	26.5
			SD	0.76	0.39	0.7	9.2	109.2	11.1
			cv	2	0.09	0.1	0.11	0.35	0.41
			95% C.I.	−6.3 to 7.1	0.84 to 7.76	2.37 to 14.83	−92.7 to 249.1	−665.1 to 1280.3	−72.2 to 125.2
30 ms	L. median	20/20	Mean	0.80	−3.50	9.1	106.2	210.4	30.3
			SD	0.87	2.06	0.7	10.3	72.8	18.3
			cv	1.12	0.6	0.1	0.09	2.89	0.6
			95% C.I.	−6.96 to 8.54	−21.84 to 14.84	2.87 to 15.33	14.5 to 197.9	−438.1 to 858.9	−132.5 to 197.7
	R. Median	20/20	Mean	0.60	3.5	9.0	101.6	169.6	29.5
			SD	0.98	1.98	0.9	14.82	72.18	14.03
			cv	1.6	0.57	0.1	0.14	0.42	0.47
			95% C.I.	−7.15 to 8.35	−14.3 to 21.3	0.99 to 17.01	−30.3 to 232.7	−473.4 to 812.6	−95.1 to 154.1

Position (x, y, and z axis—see Fig. 1C), orientation (declination and azimuth), and strength (nA).

Table 4A
Correlations of field focal amplitudes and dipole moments between two hemispheres

Scalp MEF		**M20**	**M30**	**M50**	**M70**	**M90**	**M150**	**M240**
Efflux	***r***	0.057	0.057	0.595	0.291	0.162	0.463	0.421
	p	0.009	0.009	0.015	n.s.	n.s.	0.05	n.s.
Influx	***r***	0.057	0.675	0.695	0.367	0.088	0.566	0.543
	p	0.009	0.001	0.003	n.s.	n.s.	0.014	n.s.
Dipole moment	***r***	0.27	0.308	0.673	0.635	0.126	0.248	0.036
	p	n.s.	n.s.	0.004	0.006	n.s.	n.s.	n.s.

At the early stages (M20 and M30), the SEFs between LHc (contralateral left hemisphere) and RHc (contralateral right hemisphere) were significantly correlated for both magnetic efflux and influx in MEG (***r*** for Pearson correlation, ***p*** for *P* value; significant values of $P < 0.05$ are painted in shadows, n.s. for not significant).

correlation of the dipole moments (see Table 4B) was found between the two hemispheres in the very early stages, 20M and 30M.

Correlations of field magnitudes and dipole moments within each hemisphere

Even more revealing was the consistent high correlations (r = .45–.88 and $P < 0.001$) between the extracranial magnetic fields and the intracranial dipole moments. For both hemispheres, in the early stages, 20M and 30M.

Discussion

We used a whole-head helmet in this study, and the main comparison was carried out using the laterality index of each individual subject to account for the hemispheric effects. Before measurements, we dealt with the question of head variation (see Materials and methods). The exact position under the two conditions, i.e. left hand vs. right hand stimulation, was anchored on the external landmarks. The relative amplitudes and the exact head position were well controlled, and the issue of large fall-off of amplitude in relation to head position was thus minimized. The main focus of our study was on the intra-subject difference between the two hemispheres of each subject regarding the MEG responses to unilateral median nerve stimulation. The objective of our study was, not primarily to explain differences between the evoked fields in the two hemispheres, but to identify parameters that can be used to describe the observed differences. From the results, it follows that none of the chosen parameters was in itself sufficient to describe all differences and that probably a combination is necessary in case pathologies are studied. We questioned whether there was complete hemispheric homology in activation stages, patterns, and strength of the two hemispheric responses given the unilateral stimulation on the median nerve of both hands. To that purpose, we examined the similarities and differences of the contralateral cortical responses after left and right hand median nerve stimulation in healthy volunteers. Only under the assumption of absolute hemispheric homology, it would be possible to apply the recorded activities from one intact site to infer the affected side of the brain in patients. To this end, the results of this study would contribute to elaborate a normative parameter set to be applied in clinical practice.

The number of peak stages

Although the SEF to median nerve stimulation has been studied over a decade, there is no generally accepted nomenclature yet for the description of the compressed waveform profile. From the literature, it followed that experimental settings were different with respect to the number of MEG sensors (4–306), pulse duration (0.2–0.3 ms), stimulus frequency (2.0–2.7 Hz) interstimulus interval (150–1200 ms), sampling rate (125–4096 Hz), number of trials (100–300), the time window (100–700 ms), and the off-line processing of the data (filter settings) including differences in

Table 4B
Correlations between SEFs and dipole moments within Right Hemisphere or Left Hemisphere

Efflux/moment		**M20**	**M30**	**M50**	**M70**	**M90**	**M150**	**M240**
LH	***r***	0.697	0.707	0.772	0.617	0.605	0.286	0.313
	p	0.001	0.0005	0.001	0.008	0.01	n.s.	n.s.
RH	***r***	0.629	0.778	0.621	0.755	0.564	0.288	0.099
	p	0.003	0.0001	0.005	0.0001	0.015	n.s.	n.s.
Influx/moment								
LH	***r***	−0.622	0.707	−0.881	−0.818	−0.534	0.289	0.092
	p	0.003	0.0005	0.0001	0.0001	0.027	n.s.	n.s.
RH	***r***	−0.727	0.446	−0.777	−0.582	−0.472	0.312	0.14
	p	0.0003	0.048	0.0001	0.007	0.048	n.s.	n.s.

software used to process the data. Changes in the evoked fields were shown for example to be dependent on the interstimulus interval (Wikström et al., 1997). Another source of confusion can be the orientation of the used coordinate system. Tecchio et al. (1998) used x, y, and z axes that differ from the ones used in the VSM or ASA software. In the latter software programs, the x axis is through the nose and the y axis from the left to right ear. In Tecchio's experiments, the x axis runs through the ears and the y is through the nose), their x axis is therefore 90° rotated clockwise.

Furthermore, not all authors described the parameters consistently. Kakigi et al. (2000) described, in a time window of 160 ms, 6 peak activations after median nerve stimulation. Hari et al. (1993) described, in a time window of 325 ms, 3 peak activations including SII. Tecchio et al. (1997) studied mainly the first two peaks. Wikström et al. (1997) studied peaks in a time window of 400 ms and described 4 major peaks. Lastly, Rossini et al. (1994) also worked on normative data sets and described in a time window of 50 ms the 2 major peak activations.

The present study provides maximally seven SEF stages. The nature of the individual differences remains unclear. Out of these stages, the most consistent peak activations are the 20M, 30M, 50M, 70M, 90M, and 150M. Late activation includes a 240M. The first two reflect the classical fast stages examined in the literature. Our results indicate the importance of the mid-latency and late stages in cortical response to median nerve stimulation. In fact, the largest magnitude in cerebral response to median nerve stimulation occurs at the 70M. The fast stages of 20M and 30M are known to be of somatosensory origin, while the mean latency 70M may be of sequential sensorimotor origin.

The spatial characterization of the SEFs

Two main observations of spatial organization from this study have not been reported previously. First, the regular bipolar patterns throughout the recording window as seen in Fig. 5, from early 20M to late 250M, as the MEG in the literature are often limited to a shorter window. Perhaps, the classical studies have been focused on the intrinsic sensory processing while considering the late stages as extrinsic cognitive-related potentials. In our view, the 70M, being largest in magnitude, may likely reflect the sensorimotor processing of the frontal motor stage. Additional later stages are also the continuation of sensory–perceptual processing that last from 90 ms to 250 ms in this study. The 90–130 ms being the period of SII processing, while from the 130 ms on being the SII to insular–cingulate limbic integration.

The second new observation is that, following the well-known polarity reversal between 20M and 30M, an additional and second polarity reversal between 90M and 150M is observed. First, the magnetic field in the LHc (left hemisphere) at 20 ms consisting of a dorsal negativity and ventral positivity reverses at 30 ms. The field pattern of dorsal positivity and ventral negativity remains relatively stable until about 90M, although the field strength decreases between M30 and M90, in both hemispheres. Second, between 90 ms and 150 ms, a second polarity reversal is observed. In this way, the field patterns at M20 and the M150 have approximately the same polarity, although the orientation of the fields is slightly different. The RH (right hemisphere) from M20 to M240 depicts the same double polarity reversal, but the polarities are opposite to the LH. It is as yet unclear how these changes relate to somatosensory processing between SI and SII (Hari and Forss, 1999; Kakigi et al., 2000).

Since little has been reported on the individual patterns of cortical activities, this study effectively demonstrates the great individual characteristics of cortical activation from the waveform measured in the CWP and associated topographic maps. The CWP is considered to be highly valuable in examining the hemispheric consistency of two hemispheres within the individuals and across the subjects (Tecchio et al., 2000).

Overlay plot vs. grand averaged compressed waveform profiles

Usually, only the group grand average is used to present measurements showing the main similarities across the subjects. The overlay display of the individual subjects greatly accentuates the differences among the subjects. The display of both the overlay plot and the grand average has been reported in pain research (Inui et al., 2003) The use of both plots as in Fig. 3 is advantageous, and both can be effective to convey information on brain activities.

Inter-subject and intra-subject consistency

Based on the CWP, number of stages in SEF, and amplitude parameters, our study concurs with the findings of high inter-subject variability of SEF morphology and an intra-subject interhemispheric consistency in cortical responses (Tecchio et al., 2000). In addition to the Tecchio report, this study is a major confirmation on the quantitative and normative description of the SEF values in a group of twenty healthy subjects. However, our results of the laterality index (L.I.) of focal field magnitude lend against use of sample mean (no significant difference) in comparison of two hemispherical activities. In fact, a significant minority (4/20 subjects) exhibited a right-hemisphere dominance. Our result is largely in agreement with a recent study (Jung et al., 2003) proclaiming that only a single subject (i.e. 1/16) presented a right hemisphere dominance. Their conclusion was based on the laterality of the dipole moment of the N20/SEPs only, while we examined the full spectrum from early to late phase and were likely to show a higher number of subjects with a right-hemispheric dominance. However, 2 out of 16 subjects in that report had a "pathological condition" with more than a side difference of over 50% in N20 in one hemisphere compared with the amplitude in the other (Jung et al., 2003). Our results exhibited a similar number of subjects with clear asymmetric amplitudes (4/20 at over 40%, 2/20 at 50%; see the N20 in Fig. 6). These results of "abnormality" of a 50% side difference in normal subjects may have to take into account when examining the hemispheric differences in stroke patients (Rossini et al., 2001).

The results in this study are complementary to a similar ECD study by Wikström et al. (1997). Though other studies on the unilateral stimulation of human hands were reported by SEPs (Niddam et al., 2000) and by MEG (Simões and Hari, 1999), none of them examined the laterality or homology of both hemispheres pertinent to the discussion of this study. Nevertheless, recent reports and the results of this study strongly advocate the need to examine (a) the unilateral stimulation of one hand alone, (b) unilateral stimulation of both hands independently, and (c) the relation of the hemispheric responses to hand dominance (Jung et al., 2003). In this way, we may further extent our understanding on the functional relations between hand and brain in health and in disease.

Correlation between scalp field and dipole strength

At the early stages, 20M and 30M, there was a high correlation between the observed extracranial magnetic fields and fields due to a single intracranial current dipole. In other words, a single dipole describes the source of the field adequately. The fact that there is a lower correlation at later time instants may simply reflect the fact that then more sources are active.

Between hemispheric and within hemispheric correlations of dipole moments

The results in this study of correlations (Tables 4A and 4B) of SEFs led to the unexpected finding that no correlation of the dipole moments was present between the two hemispheres in the early phase. This effect, in turn, may hamper the interpretation of dipole moments as measures of functional strengths of intact and affected brain sides. The degree of left-hemispheric predominance in sensorimotor responses in the right-handed subjects has been described recently (Jung et al., 2003) using equivalent current dipoles.

Practical implications

Any intra- and inter-individual comparison between studies requires at least the same or a comparable measuring protocol. This is true for accurately relating function and localization since the sub-areas (3a, 3b, and 1) of the human somatosensory cortex SI vary topographically to a certain extent (Geyer et al., 2000). Furthermore, we have to bear in mind that sensory activation also depends on the type of stimulated nerve (Kaukoranta et al., 1986). The results from our study may provide a step toward a normative database comprising parameters that describe hemispheric activation in response to both left and right median nerve stimulation. Such an *intra-subject interhemispheric comparison* has been established for studying the cortical reorganization in stroke patients (Tecchio et al., 2000; Rossini et al., 2001; Ossenblok et al., 2003) and is potentially useful in studies of spatial attention (Braun et al., 2002), sensory-motor gating (Wasaka et al., 2003), and writer’s cramp (Braun et al., 2003) in normal healthy subjects. But, it will also be useful for the assessment of paraplegic patients (Ioannides et al., 2002) and of chronic pain patients (Maihofner et al., 2003; Theuvenet et al., 1999). The question which parameters should be preferred to describe differences in patients after evoked cortical activation depends on the objectives of the study. In the pain studies, differences in amplitudes were measured, and the result of pain therapy was established by looking at amplitude changes. Studying differences in patient groups may provide important information for clinical practice. By way of inference from normal and pathological conditions, the results of our study are of value in order to asses abnormal activation of neuronal systems and/or brain reorganization.

Conclusion

Individual subjects exhibited unique waveform morphology in their CWP. Using complex waveform profile analysis, 6–7 peaks or stages were isolated, and the activation segments were extracted from the CWP. Intra-subject interhemispheric consistency was found in 3D topography of somatosensory evoked magnetic fields and dipole parameters. Quantitative data showed reliable consistency in latency and amplitude across the hemispheres at each peak stage. Within each activation segment, focal maximal of magnetic efflux and re-entrance could be clearly isolated. In order to assess an affected brain side, this study indicates that the following items should be taken into consideration: (a) compressed waveform profile, (b) dipole parameters related to loci, orientations, and moments, (c) laterality index, and (d) spatial topography and parameters of scalp field parameters in peak latencies, peak maxima, and peak strength. The correlations of the extracranial SEF and intracranial dipole moments in either hemisphere indicate systematic and differential processing of somatosensory information in both hemispheres. While group averages (*inter*-individual differences) tend to rule out differences, *intra*-individual characteristics are more consistent. The result of our study clearly indicates that the healthy unaffected side cannot be taken fully as the “normal reference” for the affected side of the hemisphere.

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