Neural Connectivity in Hand Sensorimotor Brain Areas: An Evaluation by Evoked Field Morphology

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Abstract: The connectivity pattern of the neural network devoted to sensory processing depends on the timing of relay recruitment from receptors to cortical areas. The aim of the present work was to uncover and quantify the way the cortical relay recruitment is reflected in the shape of the brain-evoked responses. We recorded the magnetic somatosensory evoked fields (SEF) generated in 36 volunteers by separate bilateral electrical stimulation of median nerve, thumb, and little fingers. After defining an index that quantifies the shape similarity of two SEF traces, we studied the morphologic characteristics of the recorded SEFs within the 20-ms time window that followed the impulse arrival at the primary sensory cortex. Based on our similarity criterion, the shape of the SEFs obtained stimulating the median nerve was observed to be more similar to the one obtained from the thumb (same median nerve innervation) than to the one obtained from the little finger (ulnar nerve innervation). In addition, SEF shapes associated with different brain regions were more similar within an individual than between subjects. Because the SEF morphologic characteristics turned out to be quite diverse among subjects, we defined similarity levels that allowed us to identify three main classes of SEF shapes in normalcy. We show evidence that the morphology of the evoked response describes the anatomo-functional connectivity pattern in the primary sensory areas. Our findings suggest the possible existence of a thalamo-cortico-thalamic responsiveness loop related to the different classes. *Hum Brain Mapp* 24:99–108, 2005.

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Key words: inter-district similarity; magnetoencephalography; morphology; neural connectivity individual index; SEF shape clustering

INTRODUCTION

Brain responses to sensory stimuli are characterized by time-varying spatial properties, depending on the neural circuitry involved by the specific sensory modality. Selected wiring and neuronal pools recruited in series or in parallel by the stimulated system result in a typical activation pattern of neuronal firing that shapes up the brain responses as detected by depth-implanted electrodes [Godey et al., 2001] as well as by scalp recordings [Creutzfeldt, 1977; Desmedt and Ozaki, 1991; Mauguire et al., 1997; Rossini et al., 1981,

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1987] either by electroencephalography (EEG) [Dustman and Beck, 1965; Lewis et al., 1972] or via magnetoencephalography (MEG) [Kawamura et al., 1996; Tecchio et al., 2000].

EEG and MEG detect changes of neuronal pool firing with the same time resolution of the brain processing, and discriminate the relative contribution of different relays within the neuronal network engaged by the processing of a sensory stimulus. In contrast to EEG potentials, magnetic fields generated by neural sources are not distorted by the extracerebral layers, interposed neural currents from the recording apparatus (i.e., cerebrospinal fluid, meninges, skull, and skin). Volume currents contribute little to MEG and a reference electrode, the position on which the shape of the recorded signal depends, is not needed. These three features allow the waveform of the MEG evoked responses to characterize directly the spatiotemporal properties of cerebral processing. On the other hand, MEG is only sensitive to sources tangential with respect to the scalp, and for this reason only selected neural pools, mainly pyramidal cells within sulci, will be described through magnetic field recordings.

Previous studies devoted to cerebral responsiveness of sensory hand cortical representation in unilateral stroke patients indicated unusual areas involved in the response to a somatosensory stimulation [Rossini et al., 1998, 2001]. This observation and the above-described relation between cerebral neural recruitment and shape of the generated electrophysiologic response suggested that some sort of distortion of the somatosensory evoked field (SEF) shape could be expected in those patients.

For this reason, we tried to define an index, quantifying the SEF morphologic properties in the healthy population. The main observation was that despite large inter-subject variability of the SEF shape [Kawamura et al., 1996; Tecchio et al., 2000], the interhemispheric similarity was high [Tecchio et al., 2000]. An index was defined as the correlation coefficient between SEFs in the two hemispheres in a very narrow time window (20 ms) starting with the stimulus arrival to sensory cortex (M20 onset) [Tecchio et al., 2000]. This index was found to be particularly sensitive to alterations in patients affected by monohemispheric stroke in middle cerebral artery territory [Rossini et al., 2001].

The aim of the present study was twofold: (1) to confirm and evaluate better the validity of the proposed index in describing the characteristics of somatosensory wiring responsiveness; and (2) to identify through this index individual differences of SEF shapes and provide possible prototypes. For the first aim, comparison of SEF morphology to stimulation of different districts (median nerve or fingers) was considered in the same subject. For the second aim, the hypothesis of SEF shape as an individual "fingerprint" was investigated by analyzing inter-subject shape similarity in response to median nerve stimulation and a cluster analysis was carried out to provide prototypes.

SUBJECTS AND METHODS

MEG Examination

In 36 healthy right-handed volunteers (20 men, 16 women; mean age, 38 ± 15 years; age range, 24–74 years), the magnetic field distribution over the scalp was recorded after separate electrical stimulation of the median nerve at the wrist, thumb, and little finger of left and right hands, after obtaining informed consent according to the Helsinki declaration and the approval of the local Ethical Committee. Standard electrical stimulation characteristics were used, with 0.2-ms pulses at ~ 2 Hz of repetition rate. Stimulus intensity was adjusted for the median nerve to elicit a painless thumb twitch (via surface disks) and about twice the sensory threshold for fingers (via ring electrodes). The entire recording procedure lasted about 1 hr.

Measurements were carried out using a 28-channel system operating in a magnetically shielded room (Vacuum-schmelze GMBH) [Tecchio et al., 1997]. The active channels were distributed regularly on a spherical surface (13.5 cm of curvature radius), covering a total area of about 180 cm², with a mean inter-channel distance of 2.5 cm. SEFs were recorded via a single position on the hemisphere contralateral to the stimulated side, by centering the recording apparatus on the C3/C4 positions of the 10–20 International EEG system. Data were bandpass filtered (0.48–250 Hz) and sampled at 1,000 Hz. About 300 artifact-free trials were averaged. Amplitudes of SEFs were calculated with respect to a baseline level chosen as the mean value of the 5–15 ms post-stimulus epoch.

SEF Shape Similarity Evaluation

To evaluate the shape similarity, the index *sim* was utilized. It was defined previously [Tecchio et al. 2000] and is described completely in the Appendix and sketched in Figure 1. It examines the 20-ms epoch, starting with the onset of the wave M20. Because responses are aligned in the two hemispheres to the M20 onset, morphologic characteristics in different subjects could be compared (Fig. 1b). By doing so, latency differences due to height and arm length are eliminated, and wave shape comparative analysis is therefore focused only on the epoch after the arrival of sensory input to the primary sensory cortex (M20 component generated in S1) [Hari et al., 1984; Kawamura et al., 1996; Mauguier et al., 1997; Rossini et al., 1989]. Moreover, this alignment allows comparison of responses to stimulation of different body sites (nerve and fingers; Fig. 1b).

Using this procedure, the SEF shape similarity has been evaluated for pairs of homologous body districts on the right and left side in the same subject and for median nerves of the same side in different subjects. The index comparing two SEF shapes was coded by the initials of the two stimulated districts: *sim_mt* for the similarity between SEFs after median nerve and thumb stimulation; *sim_ml* for median nerve and little finger; *sim_lt* for little finger and thumb; and

Figure 1.

Steps 1–3 for the similarity index calculation (see Appendix). **a:** Comparing median nerve SEFs in the two hemispheres of the same subject (sim_{mm}). In this case channels from the corresponding regions have opposite polarity. **b:** Comparing median nerve SEFs between homologous hemispheres in two different subjects (sim_{m,m_j}). In this case, channels from the corresponding regions have the same polarity.

sim_{mm} , sim_{tt} and sim_{ll} when comparing median nerve, thumb and little finger SEFs in the two hemispheres of the same subject, respectively. Note that sim_{mt} , sim_{ml} , sim_{lt} are calculated in the two hemispheres.

Furthermore, beyond intra-subject comparisons, inter-subject similarity of median nerve SEFs from homologous hemispheres has been evaluated. The code adopted was sim_{m,m_j} for i and j referring to the subjects, e.g., i and $j = 1,36$. In this case, the values were calculated separately for the two hemispheres. The total number of indexes corresponds to the number of pairs of subjects (i.e., $n[n-1]/2$, with $n = 36$, with a total of 630 index values for each hemisphere). All evaluated pairs are listed in Table I.

Statistical Evaluation

Because the index distribution did not result in a Gaussian shape (Kolmogorov-Smirnov test, $P < 0.001$), the following transformation allowed us to achieve the best fit: $y = \ln(1 - x)$, where $x = sim_{mm}$ (or each other sim_{mt} , sim_{ml} , ...). When expressing the results of the statistical comparisons, inverse transformation was used to obtain the same range for indexes.

The sim ability to discriminate whether the compared districts were innervated by a common nerve trunk was considered. Two shape similarity indexes were obtained for this purpose: the first (sim_{mt}) when median nerve was

TABLE I. SEF morphology similarity within and across subjects

Within subject, all indexes*									Across subjects, $m_i m_j$ **	
Right vs. left			Right			Left			Right	Left
sim_{mm}	sim_{tt}	sim_{ll}	sim_{mt}	sim_{ml}	sim_{tl}	sim_{mt}	sim_{ml}	sim_{tl}	$sim_{m_i m_{j_r}}$	$sim_{m_i m_{j_l}}$
0.96	0.87	0.87	0.91	0.85	0.80	0.89	0.86	0.82	0.74	0.77

Values given as means of each similarity index. The first three columns refer to interhemispheric similarity (left vs. right hemispheres of the same subject); all successive indexes are calculated in one hemisphere of the same (within) or different (across) subjects. m, median nerve; t, thumb; l, little finger.

* Mean = 0.88; n = 36. ** Mean = 0.75; n = 630.

compared to thumb (median nerve innervated), the second (sim_{ml}) when median nerve was compared to little finger (ulnar nerve innervated). Analysis of variance (ANOVA) for repeated measures with two within-subjects factors, both with two levels (Pair: sim_{mt} , sim_{ml} ; Hemisphere: right, left), allowed us to evaluate the differences between sim_{mt} and sim_{ml} , as well as their differences in the two hemispheres.

In addition, mean values of the different indexes of similarity within- and between-subjects were calculated and confidence intervals were constructed to reveal the presence of significant differences among them. In particular, when 95% confidence intervals (95% CI) lack overlap, significant differences ($P < 0.05$) can be assumed.

SEF Class Identification

For the definition of SEF classes, cluster analysis was carried out in the two hemispheres to compute the hierarchical cluster tree by using the complete linkage (furthest neighbor) algorithm. This method usually performs quite well in cases when the objects actually form naturally distinct "clumps." The ij element of the dissimilarity matrix was calculated by $1 - sim_{m_i m_j}$ ($i, j = 1, \dots, 36$). Note that the matrix is symmetric ($sim_{m_i m_j} = sim_{m_j m_i}$), being the i th row equal to the i th column. The clustering algorithm worked at each step by selecting the pair ij with minimal distance (maximal similarity) and by substituting the two rows i and j (column j and i) with only one row (one column). Each element of this new row was selected as the maximum between the corresponding element of the i th and j th row. In this way, the dimension of the matrix decreases of 1 at each step. Classes were identified cutting the hierarchical tree at dissimilarity of 0.4 (similarity 0.6). Prototypes were calculated as the average of individual SEF belonging to each class, after setting to 1 the M20 amplitude for each subject and aligning traces to M20 onset. The average included only cases with the same classification in the two hemispheres.

The identified prototypes were used to construct a normal range to identify those subjects showing altered SEF morphology in one or both hemispheres, without using any one of the two hemispheres as a control. "Normative" shape value was calculated by the following procedure: (1) the

similarity of each subject with each class was calculated, as the parameter $sim_{m_i p_j}$, with (in this case) m_i being the SEF of the specific subject ($i = 1, 36$), and p_j the fixed prototype ($j = 1$, number of identified classes); (2) for each subject, belonging class was selected by the prototype with maximal similarity ($sim_{m_i p_{MAXi}}$); (3) taking into account the similarity values between each subject and the class it belongs to (36 for each hemisphere = 72 values). The lower bound of the normative range, including 95% of the normative population, was calculated as $1 - \exp(\text{mean}[sim_{m_i p_{MAXi}}] + z_{0.95})$. An example of the utility of provided normative value is presented.

Localization Procedure

To discuss the physiologic significance of the different SEF morphology classes in normalcy, the localization properties of the involved component generators were considered in relation to the different classes. The localization procedure and results, without discrimination in relation to SEF classes, have been published [Pizzella et al., 1999; Tecchio et al., 1997] and we only briefly report the main steps. Starting from the SEF signal obtained as described above, equivalent current dipole (ECD) characteristics (3-D spatial coordinates, strength, and direction) were calculated. Localization algorithm was applied at 1-ms interval in the 15–50-ms post-stimulus epoch using a moving dipole model inside a homogeneously conducting sphere. The latencies corresponding to the two first maxima of the total power were considered, indicating the maximal firing synchronization of neuronal activity induced by the incoming stimulus. To identify the M30 component, the adjunctive condition of opposite magnetic field polarity respect to the M20 one was used. Localization results were accepted only if the explained variance was above 95%. The ECD position was expressed in the individual coordinate system and defined as follows: the positive y -axis was passing through the nasion and perpendicular to the plane including nasion and the two preauricular points, the positive z axis through vertex, and the positive x -axis was thus directed rightward.

RESULTS

The comparison of the SEF shapes in response to stimulation of body segments sharing (or not sharing) peripheral

Figure 2.

SEF signals from all parietal channels are superimposed in the 100 ms after the separate stimulation of right median nerve, thumb, and little finger in one representative subject. The median nerve SEF shape is much more similar to thumb than to little finger ($sim_mt = 0.95$, $sim_ml = 0.35$).

innervation, i.e., median nerve with thumb (sim_mt) and median nerve with little finger (sim_ml), showed significantly higher similarity for the former (sim_mt) with respect to the latter (sim_ml) condition ($F[1,24] = 5.813$; $P = 0.024$). A representative example is shown in Figure 2. No significant difference between the two hemispheres was found and the difference between couples did not differ in the two hemispheres (interaction of Couple $\times$ Hemisphere was not significant).

SEF shapes for different districts in the same subject (sim_mt , sim_ml , sim_tl in left and right hemispheres, sim_mm , sim_tt , sim_ll , Table I), were significantly more similar than were homologous districts compared in different subjects (sim_m_i , m_j in left and right hemispheres, legend in Table I, Fig. 3a, and sim_m_i , m_j vs. ALL in Fig. 3b). In particular, the average similarity of median nerve SEF in the two hemispheres (sim_mm) was observed to be significantly higher than was wave morphology similarity from stimulation of different districts of the same subject (Fig. 3b, sim_mm vs. ALL).

The SEF similarity levels in different subjects showed a wide scatter: the minimum and maximum values for sim_m_i , m_j parameter were -0.68 and 0.99 , respectively, with mean $= 0.75$ with respect to the range $0.79-0.99$ (with mean 0.96 for sim_mm). This wide range of sim_m_i , m_j was due to some pairs of subjects with very similar and some with very different SEFs shapes. In particular, negative values indicate that in a given time interval, the two subjects presented a phase reversal. These features suggest that there may exist subgroups of subjects with similar SEFs; in line with this, we used sim to construct SEF shape similarity classes. Cluster analysis enabled us to identify four main classes in the left hemisphere (A–D), when cutting the similarity level to 0.6, as delineated in Figure 4. At this level, classification coincided in the two hemispheres in 78% of cases (Table II); in particular, no subject was classified in class D in both hemispheres, thus producing three main classes. Their class prototypes were then constructed (Fig. 5).

These prototypes were used for detecting subjects with altered SEF shape. The normative value calculated as de-

scribed above was determined to be 0.69. If a subject showed SEF in one or both hemispheres, less similar than 0.69 to the class prototype, the SEF shape was considered abnormal. To test this assumption, tracings from three patients affected by a monohemispheric ischemic lesion characterized by abnormal SEF interhemispheric asymmetry were utilized. The SEF from the affected hemisphere was classified as altered from the point of view of the newly introduced parameter, which does not involve a comparative analysis with the unaffected hemisphere (Table III).

The different morphology prototypes showed a strong difference in the time evolution of the M30 shape, once normalized for the M20 amplitude. We investigated whether this shape variability could be accounted for by anatomic characteristics of the central sulcus. This was tested by means of position and directions of the activated cerebral sources. In particular, our aim was to check if subjects belonging to different classes showed different source characteristics of M30 with respect to M20 component. From a statistical point of view, this corresponds to assess the significance of the interaction of Class $\times$ Component. For such a purpose, ANOVA for repeated measures were applied twice, the first for Position, the second for Direction of the M20 and M30 ECDs. The within-subject factors were Component (M20, M30) and Hemisphere (Right, Left). The between-subject factor was Class (A and B; class C was excluded because component M30 was not identifiable). Because each position and direction can be measured on three axes (x , y , z), these three measures were defined in the doubly multivariate ANOVA. According to Pillai's trace statistic (Table IV), Component, Hemisphere, and Component $\times$ Hemisphere resulted significant for Position measures, Component resulted significant for Direction measures (Component $\times$ Hemisphere reached a P value of 0.052). In particular, we observed that: (1) M30 ECD was more medial than was M20 ECD in both the hemispheres and in both classes, the difference between the two components in terms of mediolateral coordinate was larger in the left than in the right hemisphere, and both generators (of

Figure 3.

a: The same organization as in Figure 2. SEF morphology differs significantly in the two representative subjects, whereas they are very similar for different stimulated districts, also when the innervating nerve is different (median nerve for thumb, ulnar for little finger) (Subject 1, $sim_{mt} = 0.91$, $sim_{ml} = 0.91$; Subject 2, $sim_{mt} = 0.97$, $sim_{ml} = 0.92$; $sim_{m_i, m_j} = 0.79$). **b:** Interval centered on the mean across all subjects and hemispheres of the

following indexes: in the same subject, $sim_{mm} =$ left vs. right median nerve and $ALL = sim_{mt}, sim_{tt}, sim_{ll}$, and $(sim_{mt}, sim_{ml}, sim_{lt})$ in the two hemispheres; in different subjects, $sim_{m_i, m_j} =$ median nerve of Subject i and median nerve of Subject j in the homologous hemisphere. Intervals are wide four times the standard errors, and their disjunction indicates the 95% significance of the respective group difference.

M20 and M30) were more anterior in the right hemisphere with respect to the left in both classes; and (2) M30 direction was opposite to M20 in both classes and hemispheres. It is worth noticing that the relative directions of M20 and M30 generators were not different in the two classes (no interaction of Class $\times$ Direction).

DISCUSSION

The index investigated in the present study demonstrated that the shapes of brain responses to sensory stimuli from the hand and fingers were more similar for districts with common

peripheral nerve innervation than for districts with different innervation. On the one hand, this indicates that the morphology of an evoked response is linked to the anatomo-functional neural pattern of peripheral-central connectivity, and on the other hand, indicates that the defined index enables these morphologic properties to be evaluated quantitatively.

The somatosensory system connectivity, as reflected presently by SEF morphology, is characterized by a significant inter-individual variability, not only in the late components generated in central-parietal associative areas [Kawamura et al., 1996; Tecchio et al., 2000], but also in those at very brief

Figure 4.

Clustering tree, showing the degree of similarity among different subjects. In the left hemisphere, average SEF across all subjects in the branch are indicated. Four main groups are identified by cutting at 0.4 distance.

latencies (<45 ms) generated in primary somatosensory areas. This variability probably reveals inter-subject differences of the peripheral-central network connectivity, related to parallel/serial activation balance among post-central Brodmann's areas 3b, 1, 2, and the precentral area 4 within the thalamo-cortico-thalamic loop. High levels of intra-individual median nerve interhemispheric similarity, however, suggest that handedness does not affect much the spatio-temporal properties of the primary network activation induced by stimulation of the dominant and nondominant hand.

In the present study, the SEF morphology was found more similar between different hand districts compared in the same subject than in different subjects, underlining its relationship with the substrate of the cortical relay activation profile. Furthermore, this finding suggests that the SEF morphology could be a specific characteristic of each individual.

The presence of three main SEF morphology classes offers the opportunity to add evidence of the contribution of dif-

ferent cortical areas to each component. The variability is found once having normalized for the M20 amplitude; that is, after having frozen the responsiveness of the neuronal pool marker of the stimulus arrival in S1, and focusing on responsiveness of the following neuronal pools.

Figure 5.

Prototypes of the 3 classes (A, B, and C). Class A, including most subjects (18 of 29 selected for prototype calculation), was characterized by short M20 and long-lasting M30, larger in amplitude than M20. Class C (3 of 29) was characterized by longer M20 and M30 not inverted in polarity with respect to M20. Class B (8 of 29) was in-between, with M30 inverted in polarity with respect to M20.

TABLE II. SEF shape classification for the two hemispheres

Right hemisphere	Left hemisphere			
	A	B	C	D
A	18	—	—	—
B	4	8	—	2
C	—	—	3	—
D	—	1	—	—

Number of subjects classified in each class on the base of SEF from the two hemispheres. On the diagonal, subjects with the same classification in the two hemispheres (78%). No subject falls in the same class D in the two hemispheres.

TABLE III. Interhemispheric similarity and hemispheric classification in patients

Cases	<i>sim_mm</i>	Hemisphere	
		Unaffected	Affected
S1	0.36	0.96	0.58
S2	0.46	0.90	0.52
S3	0.04	0.97	0.18

Three patients affected by a monohemispheric lesion, with the interhemispheric morphology similarity index (*sim_mm*) out of normative limits (0.76; [Tecchio et al., 2000], values in bold). In the unaffected hemisphere, the SEF belonged to class A, whereas in the affected hemisphere, the SEF belonged in two cases to class B (S1 and S2); for all three, the similarity index with the belonging class prototype was out of normative range.

At the present stage, we suggest that the M20 generator is constituted mainly of neuronal pools in Brodmann's area (BA) 3b, due to prevalence of tangentially oriented neurons contributing to MEG signals [Hari et al., 1984; Mauguire et al., 1997; Rossini et al., 1989; Tecchio et al., 1997]. The M30 component is considered to be generated mainly by BA 4, on the base of M30 opposite direction with respect to the M20 generator, the independent behavior in patients affected by a cerebral lesion [Rossini et al., 2001] and, most importantly, different subtending source positions with respect to M20 [Huang et al., 2000; Kawamura et al., 1996; Tecchio et al., 1997; present findings]. We speculate that subjects belonging to class C would be characterized by low connectivity to BA 4 and BA 4 low activation. In fact, their SEFs are characterized by M20 polarity lasting throughout the 20-ms time interval from M20 onset.

Another possible explanation for the difference found among subjects belonging to different SEF morphology

classes was related to anatomic variability. As there are evidences cited above, supporting separate generators for M20 and M30 components, differences in central sulcus shape among classes could subtend the loss of sensitivity to the field generated by the second component. It is to be noted that on the basis of the hypothesis of M20 from BA 3b and M30 from BA 4, the variability has to regard the relative displacement of the upper bank of the central sulcus with respect to the posterior bank, as the differences in shape regard the M30 component, once "normalized" for the M20. The direction of the M20 and M30 ECDs were not statistically different (unless being opposite), and this behavior was preserved in different classes. Although we could define only the direction of a given source for its component tangential to the scalp, because of MEG sensitivity only to tangential sources, it remains quite improbable that in different classes only the "radiality" of the component is changing.

A third possibility in M30 intensity variability is related to the hypothesis of Wikstrom et al. [1996] of M30 as expression of BA 3b inhibitory postsynaptic potentials (IPSP). In this possibility, the variability found is interpreted as intra-individual variability in the intracortical connectivity, inducing a reduction in inhibitory feedback circuitry efficiency.

Future studies are needed to correlate class of SEF shape with other physiologic and anatomic group features. The present work provides an index enabling identification of alterations in sensory cortical activation without the need to use the other hemisphere as a control. This could be useful in situations involving bihemispheric lesions.

In addition, the lowest variability for the interhemispheric median nerve similarity has been confirmed [Tecchio et al., 2000]. This is a powerful indicator to possibly detect unilateral abnormalities in the activation pattern due to unilateral

TABLE IV. Statistical analysis on position and direction of M20 and M30 sources

Parameter	Interaction	Pillai's trace	<i>F</i> (3,14)	<i>P</i>
Position				
Between subject	CLASS	0.297	1.969	0.165
Within subjects	COMP	0.626	7.808	0.003
	COMP * CLASS	0.398	3.087	0.062
	HEM	0.78	16.536	0.000
	HEM * CLASS	0.362	2.645	0.090
	COMP * HEM	0.426	3.467	0.045
	COMP * HEM * CLASS	0.127	0.676	0.581
Direction				
Between subjects	CLASS	0.387	2.522	0.107
Within subject	COMP	0.982	216.375	0.000
	COMP * CLASS	0.064	0.272	0.845
	HEM	0.212	1.074	0.397
	HEM * CLASS	0.071	0.306	0.821
	COMP * HEM	0.462	3.433	0.052
	COMP * HEM * CLASS	0.189	0.930	0.456

Pillai's trace coefficient and corresponding *F* and *P* values for main and interactive effects. Values in boldface highlight significant (*P* < 0.05) factors.

cerebral lesion, or when unilateral peripheral nerve inflow alterations occur.

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APPENDIX

The index (*sim*) chosen to evaluate the shape similarity of fields evoked by two different somatosensory stimulation is defined as follows (step numbers and labels according to Fig. 1):

1. The two channels with opposite polarity and maximal amplitude in each hemisphere are selected;
2. The channels in the two hemispheres are aligned to M20 onset and the correlation coefficients of each channel with the one in the corresponding cerebral region of the other hemisphere are calculated, in the time period lasting 20 ms from M20 onset;
3. These two correlation indexes are averaged.

The calculus thus is

$$sim = \pm \frac{1}{2} \left[\left(\frac{\sum_{i=1}^{20} x_i y_i}{\sqrt{\sum_{i=1}^{20} x_i^2 \sum_{i=1}^{20} y_i^2}} \right)_{vertex} + \left(\frac{\sum_{i=1}^{20} x_i y_i}{\sqrt{\sum_{i=1}^{20} x_i^2 \sum_{i=1}^{20} y_i^2}} \right)_{temp.par} \right]$$

where *x* and *y* are the four channels, each pair in the corresponding cerebral regions more proximal to vertex (*vertex*) and in the temporoparietal (*temp.par*) areas respectively. When comparing left to right hemispheres (Fig. 1a, *sim_{mm}*) the index is multiplied by minus one, because the channels in the two corresponding cerebral regions (vertex and temporoparietal) have opposite polarities. When comparing re-

sponses from the same hemisphere or homologous hemispheres in the same subject (Fig. 1b, sim_{m_i, m_j}), the channel pairs have the same polarities and the sign is not changed.

The rationale for the choice of minimum/maximum channels, at the latency of the first component around 20 ms, is to be maximally sensitive to the onset of the cerebral response to the median nerve/fingers stimulation. Indeed, the first component around 20 ms is accepted as the marker of the signal arrival in the primary sensory areas. Moreover, a consistent dipolar distribution is generated at this peak latency and the minimum/maximum channels are the best activation descriptors. A time window lasting 20 ms is chosen to focus the analysis on the activation properties of the neural network within the primary sensorimotor areas; this period includes the two first response components (M20 and M30), generated mainly in these cortical regions. M20 and M30 sources are very near each other and the minimum/maximum chan-

nels defined on M20 are also well representative for the M30 component.

Obviously, due to spatial sampling, the channel chosen as the maximum (minimum) is not in general the real maximum (minimum) point of the distribution. In this respect, we provide evidence that variations of recording system positioning in different sessions, and consequently different sampling positions, induce negligible variation of the index. The coefficient of variation (CV) for five sessions in different days in the same subject resulted (< 0.001).

As a consequence of the index definition, the maximum value is 1, corresponding to identical shapes, with at most an amplitude scale difference. The minimum value could not reach -1 , because by definition in approximately the first quarter of the examined epoch, the two traces must have the same polarity resulting in a positive covariance.

Note that sim_{mm} coincides with IHC_S1 of Tecchio et al. [2000].