Somatotopy in Human Primary Motor and Somatosensory Hand Representations Revisited

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High-resolution functional magnetic resonance imaging of healthy volunteers was used to study the functional anatomy of the human primary motor (M1) and somatosensory (S1) cortical hand representations during simple movements of thumb, little finger and wrist and a sequential movement of the middle three fingers. Rest served as a control state. The results demonstrated an orderly somatotopy in both M1 and S1, even though the cortical areas active with individual movements significantly overlapped. Moreover, the activation patterns in M1 and S1 differed in three aspects: (i) S1 activation was distributed into significantly more clusters than M1 and the primary cluster was smaller; (ii) the overlaps of areas active with different movements were significantly larger in M1 than in S1; (iii) the difference between the three-finger sequential movement and the single-finger movements was more pronounced in S1 than in M1. The sequence-activated S1 cortex was distributed into significantly more clusters. There was also a trend for a bigger volume difference between sequence and the single finger movements in S1 than M1. These data suggest that while the distributed character dominates in M1 and S1, a somatotopic arrangement exists for both M1 and S1 hand representations, with the S1 somatotopy being more discrete and segregated, in contrast to the more integrated and overlapping somatotopy in M1.

Introduction

Although the functional organization of hand representation in human primary motor (M1) and somatosensory (S1) cortices has been studied since the observations of spreading motor and sensory seizures in epilepsy patients (Hughlings Jackson, 1863) and electrical stimulation of precentral and postcentral cortices (Foerster, 1931; Penfield and Boldrey, 1937), a clear consensus has not yet emerged. There has been an agreement from different research modalities that the cortical representations of movement are distributed over wide areas of cortex. There is also converging evidence that the major sub-divisions of M1 and S1 representing head, arm, trunk and leg are located in a latero-medial sequence along the precentral and postcentral gyri. On the other hand, there is less agreement on the organization within the hand/arm sub-divisions.

A number of recent studies of human M1 hand and arm representation have confirmed the distributed character as well as the basic somatotopic arrangement suggested by Foerster (Foerster, 1931) and Penfield and Boldrey (Penfield and Boldrey, 1937), using various non-invasive mapping methods: positron emission tomography (Grafton *et al.*, 1993; Kawashima *et al.*, 1995), functional magnetic resonance imaging (fMRI) (Rao *et al.*, 1995), trans-cranial magnetic stimulation (Wassermann *et al.*, 1992; Wilson *et al.*, 1993) and magnetoencephalography (Cheyne *et al.*, 1991; Erdler *et al.*, 1999). However, not all studies support this picture. Volkmann and co-workers found clearly separable sources for different finger movements but no somatotopy (Volkmann *et al.*, 1998). Major spatial overlap of movement representations and no evidence for somatotopy were found in an fMRI study of finger and wrist movements (Sanes *et al.*, 1995). Reviewing the detailed data from human and non-human primate literature, Sanes and Donoghue concluded that the arm sub-division of M1 is a highly distributed network where movements and/or muscles are intermingled without somatotopy as the main organizing principle (Sanes and Donoghue, 1997). Still, a recent high-resolution fMRI study (Kleinschmidt *et al.*, 1997) suggested the existence of a somatotopic gradient for simple finger movements in the presence of significant overlaps in the human M1, even though the single available slice through M1 provided very limited evidence.

Recent functional mapping studies of human S1 hand representation using fMRI (Maldjian *et al.*, 1999), magnetoencephalography (Hari *et al.*, 1993; Nakamura *et al.*, 1998) and somatosensory evoked potentials (Buchner *et al.*, 1995) have also confirmed the orderly and separable somatotopy found in earlier human studies (Foerster, 1931; Penfield and Boldrey, 1937) as well as in non-human primates (Kaas *et al.*, 1979), although other studies have reported a more complex arrangement in monkeys (Juliano *et al.*, 1981; McKenna *et al.*, 1982) as well as in humans (Gelnar *et al.*, 1998). Furthermore, most S1 studies have used vibratory stimuli or (unnatural) electrical stimulation. At present there are no mapping studies of S1 activity related to human proprioceptive feedback during voluntary hand movements and in non-human primates the data are less extensive than for other somatosensory modalities (Kaas *et al.*, 1979; McKenna *et al.*, 1982; Recanzone *et al.*, 1992). The existence of four sub-areas of primate S1 introduces additional complexity, although the hypothesized maps of S1 sub-areas seem to be aligned in parallel (Kaas *et al.*, 1979).

In the present study we have used high-resolution fMRI to investigate further the nature of the somatotopic arrangement of hand movements in M1 and S1. We hypothesized that the structure of these cortical regions would reflect concurrently both somatotopy and distributed overlaps among different movement representations.

Materials and Methods

Subjects and Tasks

We studied 11 healthy right-handed volunteers (eight men and three women, age range 23–34 years, mean 27.2 years) without any history of neurological or developmental illness. All were right-hand dominant according to the Edinburgh Inventory (Oldfield, 1971) with a laterality score of 0.76 ± 0.20 and gave their informed consent prior to the study, according to a protocol approved by the University of Maryland Institutional Review Board. Mapping of brain function was performed using blood oxygenation level-dependent (BOLD) fMRI during performance of four different hand movements and rest. Subjects used their non-dominant left hand to perform blocks of simple repetitive flexion–extension movements of thumb (Thumb), little finger (Little) and wrist (Wrist), successive finger flexion via a six digit keypad sequence using the

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three middle fingers (Sequence) and rest. Specifically, the sequence involved pressing the keys 1–6–8–3–9–4 on a numerical keypad. Movements were paced at 2 Hz by short beeps heard in pneumatic headphones. High frequency beeps marked the periods of hand movement, while low beeps were presented during rest periods. Task blocks were 24 s long, separated by 6 s breaks. Blocks of movements were performed in different random orders during each of five 10 min runs, with the order of movements counterbalanced across runs. Subjects received instructions about the type of movement to be performed over headphones during the breaks between movements and kept their eyes closed throughout the experiment. Subjects practiced the movements and keypad sequence briefly before the first scan to make certain they could perform the movements at the required rate.

MRI Data Acquisition

MRI data were acquired on a 1.5 T Signa scanner (GE Medical Systems, Milwaukee, WI) with a standard head coil. Twelve oblique axial slices were prescribed parallel to the intercommissural (AC–PC) line and adjusted to cover the superior part of the cortex, including the superior convexity. Anatomical images were T_1-weighted [550 ms repetition time (T_R), 6 ms echo time (T_E), 70° flip angle, two excitations, spin echo]. Functional (T_2*-weighted) data used BOLD contrast and were acquired with the four-shot spiral technique (Noll *et al.*, 1995, 1999) with 60° flip angle, T_E = 35 ms and T_R = 1500 ms per spiral, providing 1.6 × 1.6 (in-plane) × 3 mm (slice thickness) resolution. Two scans were added at the beginning of each functional scanning series (run) and the data discarded to eliminate the transient behavior of the scanner and reach a steady-state before acquisition of the experimental data. Scanning started 3 s after the experimental paradigm to compensate for part of the hemodynamic delay. We also acquired 2-D phase contrast magnetic resonance angiography data sensitized to slow venous flow (gradient echo, 25° flip angle, 6 ms T_E, 25 ms T_R, 192 × 256 matrix, velocity encoding 10 cm/s, sensitive to all flow directions). Slice locations exactly matched the functional and anatomical scans. A 3-D T_1-weighted spoiled gradient echo volume scan (6 ms T_E, 24 ms T_R, 40° flip angle, 124 slices, slice thickness 1.5 mm, FOV 24 cm, 192 × 256 matrix) provided thin slices to allow identification of the neuroanatomy with high resolution in all three orthogonal planes.

Spiral image reconstruction was performed off-line on a SGI Origin2000 server (Silicon Graphics, Mountain View, CA). Automated Image Registration (AIR) v.3.0 software (Woods *et al.*, 1998) with a 3-D rigid model and least squares cost function for alignment and a trilinear model for reslicing was used on the functional images to correct for movement within and between experimental runs. For AIR, data were Gaussian blurred during the estimation phase with 1.6 mm full-width at half-maximum. The reference T_2* image volume was chosen to be in the middle of the third out of five experimental runs to minimize the necessary alignment. The in-plane anatomical images and angiograms were registered to the same reference using AIR with a 3-D rigid model and variance ratio cost function for alignment and a trilinear model for reslicing. For phase contrast angiograms alignment was performed using a flow enhanced set of images; the estimated correction was then applied to the background-suppressed vascular images from the same acquisition. Skull and meninges were manually segmented out prior to cross-modality registration. Anatomical landmarks visible in all modalities (such as cortical sulci and, especially, the central sulcus) were used to evaluate the success of the cross-modality registration. If a residual in-plane displacement of the registered image against reference was found, the registered images were manually shifted in-plane to the correct position. This manual correction never exceeded 1 voxel. Functional data from the top and bottom slices were excluded from analysis because of interpolation artifacts from image registration.

Voxel-by-Voxel Analysis

Voxel-by-voxel analysis was performed using the MCW AFNI package (Cox, 1996) to calculate cross-correlation of the detrended vector of signal intensities over time with a modified sinusoidal model waveform (Bandettini *et al.*, 1993) using positive and negative half-sinusoids in the position of the task blocks selected for comparison. The time points acquired during 6 s breaks and the task blocks not involved in the current comparison were excluded from the waveforms. In order to minimize false positives, a combination of a single voxel statistical threshold r = 0.37 and a 3-D contiguity threshold (Forman *et al.*, 1995) of 3 voxels (volume ~ 22 mm^3) was used to determine which voxels were active. These values were chosen based on the results of Monte Carlo simulations from the MCW AFNI package that determined these values to provide an overall (whole brain) α level <0.05.

Vascular artifacts (voxels activated as a result of macroscopic venous blood flow) were removed using a mask based on magnetic resonance angiograms (Hluštík *et al.*, 1998). Briefly, the angiograms were Gaussian blurred to the resolution of the T_2*-weighted images and thresholded at the mean + 2 SD to create a binary image of draining veins. Activation co-localized with the venous mask was removed.

Regions of Interest

Regions of interest were defined *a priori* on axial anatomical T_1-weighted images using MNI-Display software (Montreal Neurological Institute, Montreal, Canada). The primary motor cortex was identified on the anterior bank of the central sulcus and, in the most superior slices (above the level of the confluence of precentral and superior frontal gyri), also on the posterior part of the precentral gyrus. Here the precentral gyrus was traced from within the central sulcus out to the most lateral point on the convexity, which was used as the anterior limit of M1 (Rademacher *et al.*, 1993). The primary somatosensory cortex was outlined on the postcentral gyrus to include areas 3a, 3b, 1 and 2 using the precentral and postcentral sulci as delimiting landmarks (Brodmann, 1909; Geyer *et al.*, 1999).

Somatotopy and Spatial Complexity

For all significantly activated voxels in M1 and S1 both centers of mass (COMs) and volumes of activation were calculated for each movement–rest comparison. For COM calculation the contribution of each voxel was weighted by its correlation coefficient to enhance the contribution of voxels containing a greater proportion of active tissue. When the movement representation consisted of multiple non-contiguous clusters, the global center of mass was again calculated as a weighted average, using the average correlations for each cluster as the weights. To assess the spatially distributed nature of activated M1 and S1 cortex for each movement, we calculated the number of clusters of significant activation (cluster count) and the percentage of total ROI volume activation contained in the largest cluster (primary cluster). To assess the degree of overlap between cortical representations of individual movements, the volume of cortex shared by two different movements was expressed as the percentage of the area activated by either of the movements. Measuring the 3-D (Euclidean) distance of the extreme ends of an area including voxels activated with any finger movement (Thumb, Little or Sequence) provided an estimate of the sizes of the M1 and S1 hand representations.

Statistics

Group results are reported as means ± SD. For evaluation of somatotopy, repeated measures analysis of variance (ANOVA) was performed to assess the effect of movement type on each of the three spatial coordinates that specify the COM in the medial–lateral (x), anterior–posterior (y) and inferior–superior (z) directions. Similar ANOVAs were performed on the volumes and complexity measures. Where a significant main effect of movement was found, individual movements were compared pairwise using the Student–Neuman–Keuls (post-hoc) test. An α level of 0.05 was used for all statistical tests.

Results

M1 Somatotopy

Right M1 (contralateral to the moving hand) was significantly activated in all 11 subjects with all four movements. Individual movements activated similar M1 areas around the knob demarcating the hand region (Yousry *et al.*, 1997) and the movement representations overlapped in a significant way (Fig. 1). The average centers of mass of M1 activation produced

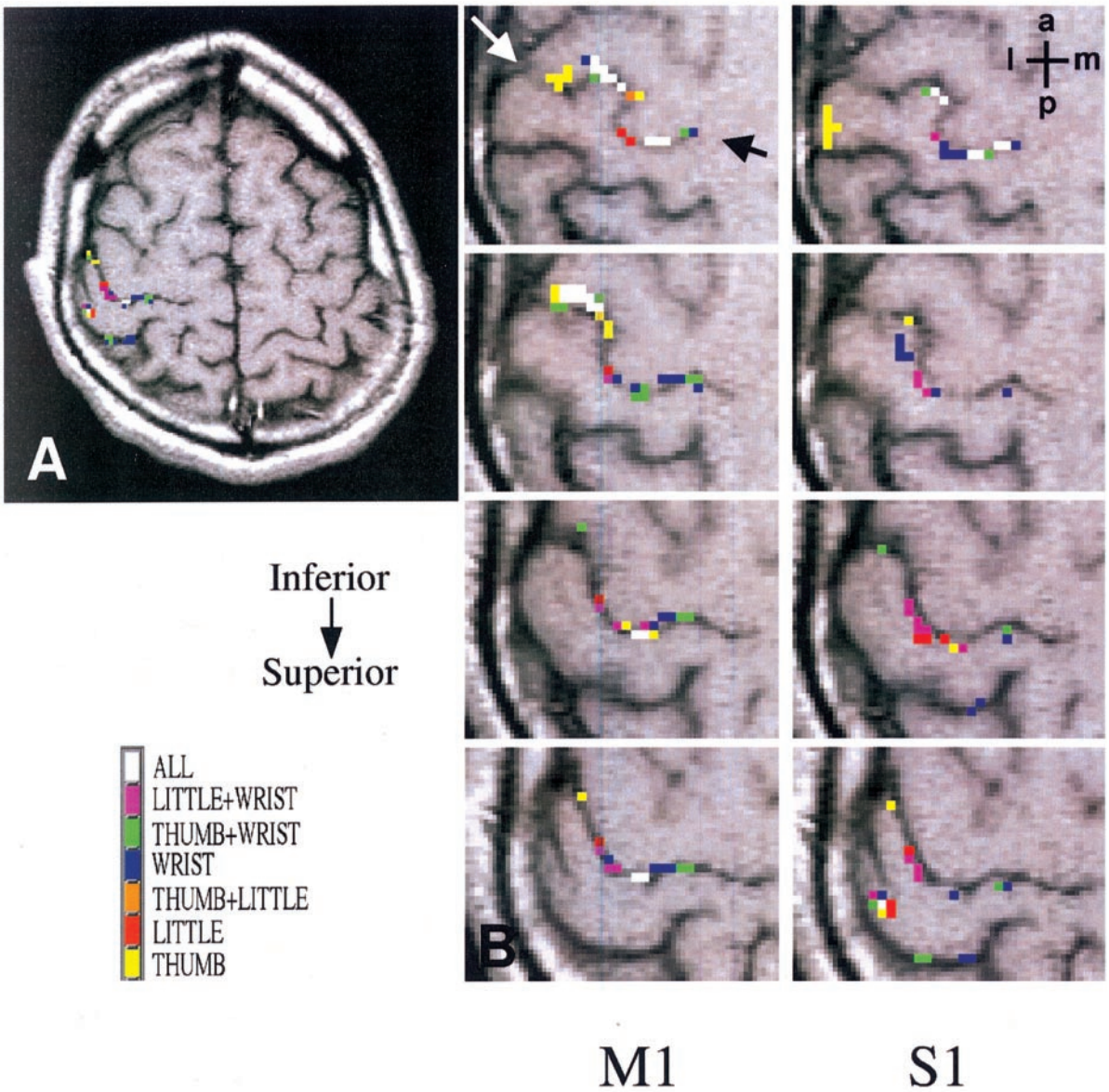

Figure 1. Overlaps of representations of simple movements (repetitive flexion–extension of thumb, little finger and wrist, respectively) in primary motor and somatosensory cortices in one subject that shows somatotopy. Significant brain activation with individual movements and their overlaps are superimposed on structural magnetic resonance images of the same axial slices. (*A*) M1 and S1 activation in one slice. (*B*) Detailed arrangement in M1 and S1 contralateral to the moving hand in four adjacent slices. In each column of (*B*) activation in other regions was masked out for clarity. Slice orientation is indicated in the top right corner. a, anterior; p, posterior; m, medial; l, lateral; arrows denote the central sulcus.

by the four movements compared to rest were found to lie approximately in the somatotopic order suggested by Penfield, with thumb, sequence, little finger and wrist positioned progressively more medially, posteriorly and superiorly along the course of M1 (Penfield and Boldrey, 1937) (Fig. 2*A*,*B*).

When only the simple (non-sequential) movements of the thumb, little finger and wrist were considered, most individual subjects (10/11) showed the predicted order of COMs in at least one direction (x, 7/11; y, 6/11; z, 3/11).

The type of movement was found to have a highly significant effect on two out of three spatial coordinates of the M1 activation COM [x, $F(3,30) = 11.3$, $P = 0.0001$; y, $F(3,30) = 7.0$; $P = 0.0011$] and approach significance for the third [z, $F(3,30) = 2.9$, $P = 0.052$; repeated measures ANOVA]. Pairwise comparisons of individual movements revealed significant differences in location between Thumb and Wrist (in x, y coordinates), Thumb and Little (y), Sequence and Little (y), Sequence and Wrist (x, y) and Little and Wrist (x only).

The mean 3-D distance between Thumb and Little COMs was 2.5 ± 2.0 mm and between Thumb and Wrist 4.0 ± 3.7 mm. Although the centers of mass of the activated regions demonstrated a somatotopic arrangement, the regions active during different movements overlapped significantly (Fig. 1).

Activation was also observed in the left (ipsilateral) M1 during sequential movement (10/11 subjects) as well as during thumb (4/11), little finger (6/11) and wrist (7/11) movement, but no statistically significant somatotopy was detected.

S1 Somatotopy

The right S1 region (i.e. contralateral to movements) was also activated in all subjects and all movements except for one subject's Thumb. For S1 an analysis identical to that performed

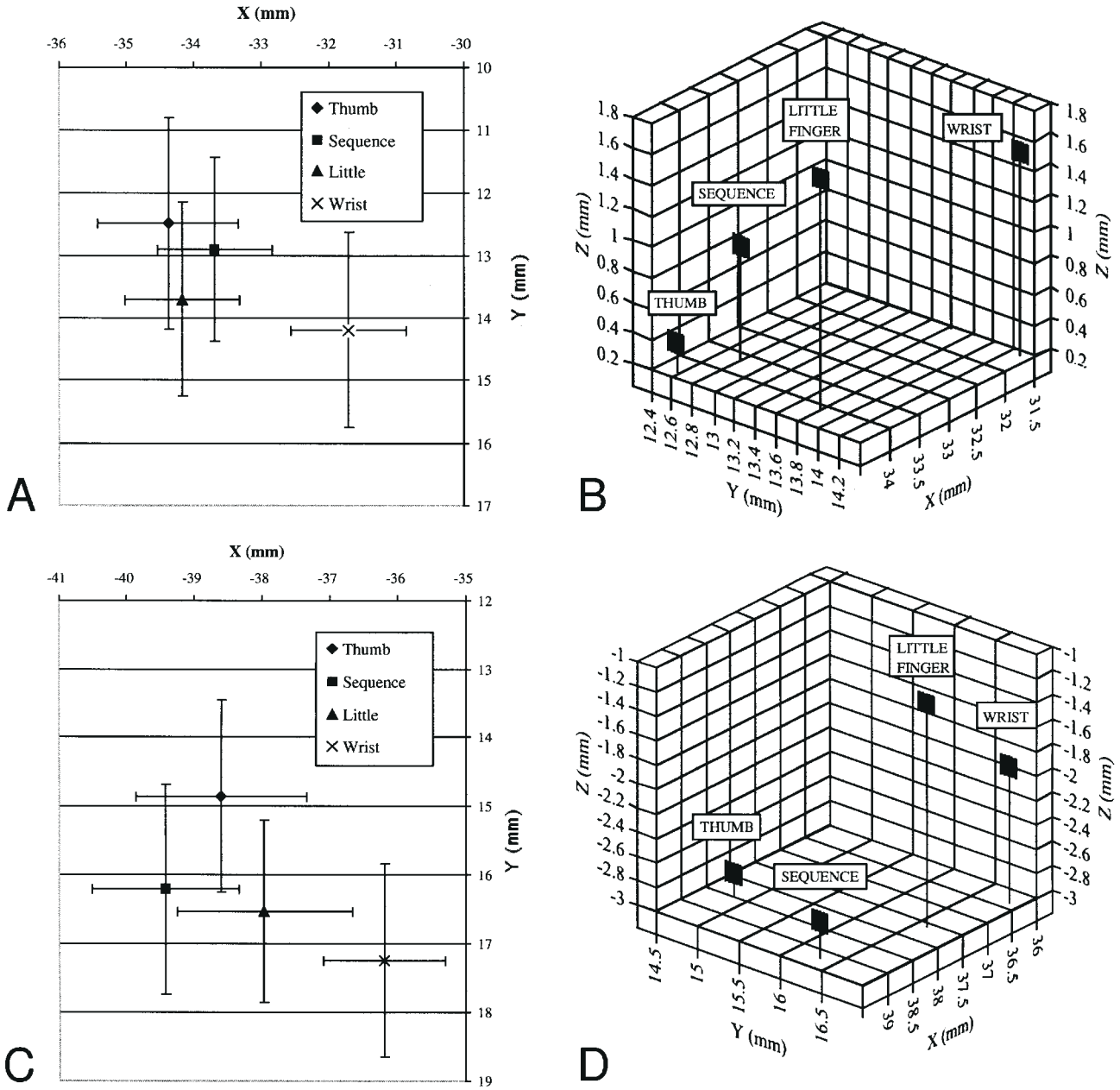

Figure 2. Somatotopic arrangement of the centroids of primary motor and somatosensory representations of different hand movements. (*A*,*B*) Primary motor cortex. (*A*) Position of centroids projected to the axial plane corresponding to slices shown in Figure 1. (*B*) A 3-D view of the same data. (*C*,*D*) Primary somatosensory cortex. (*C*) Centroids projected to the axial plane. (*D*) A 3-D view. Horizontal axis, medial (right) to lateral, centered on the mid-sagittal plane. Vertical axis, anterior (top) to posterior, centered on the center of the imaged section. Data represent group means ± SEM.

for M1 also revealed spatially distinct COMs at a high level of significance [x, $F(3,27) = 8.8$, $P = 0.0003$; y, $F(3,27) = 5.0$, $P = 0.0069$; z, $F(3,27) = 6.2$; $P = 0.0023$, repeated measures ANOVA]. Analysis of individual movements revealed significant pairwise differences in comparison of Thumb and Little (y, z coordinates), Thumb and Wrist (x, y), Thumb and Sequence (y), Sequence and Little (x, z), Sequence and Wrist (x) and Little and Wrist (x).

The average centers of mass of S1 activation produced by the four movements compared with rest were found to lie in a somatotopic order similar to M1 (Fig. 2*C*,*D*). A majority of subjects (eight of 11) showed the predicted order in at least one direction (x, 6/11; y, 5/11; z, 2/11) for the thumb, little finger and wrist only (not counting the sequence) and three subjects (x, 0; y, 2; z, 1) when all four movements were counted. The COM for sequential movement was located on average more laterally than that of the thumb, which may be attributed to the curved course of the precentral gyrus (Fig. 1).

The 3-D distance between the Thumb and Little COMs was 3.2 ± 1.6 mm and between Thumb and Wrist 3.5 ± 2.2 mm. As in M1, the spatial extent of the regions active with different movements overlapped, but the overlaps were all significantly smaller than those in M1 (Fig. 3*D*).

As in M1, activation was also observed in the ipsilateral S1 during sequential movement (9/11 subjects), thumb (4/11), little finger (2/11) and wrist (3/11) movement but the limited amount

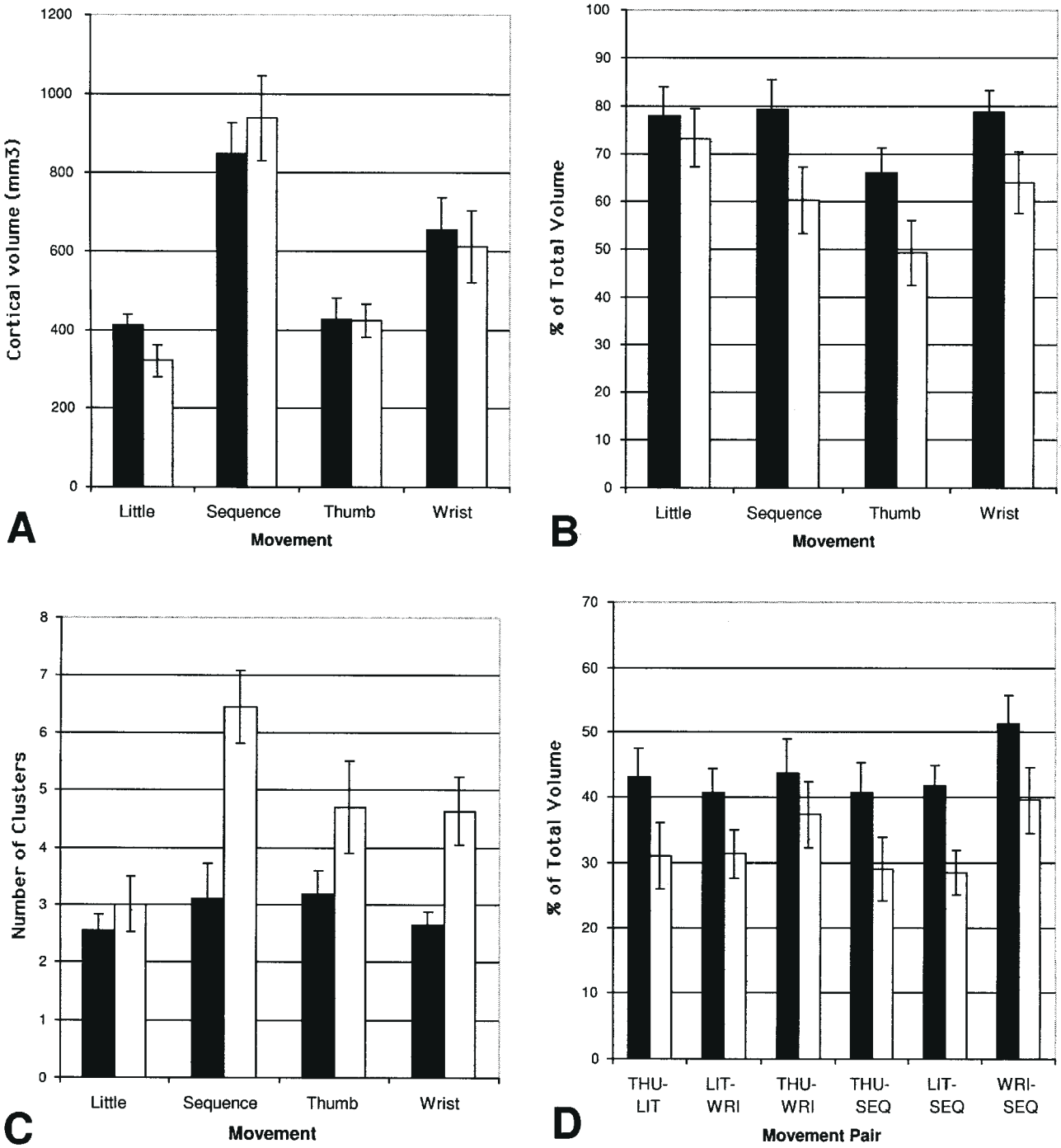

Figure 3. Functional organization of hand movements in the primary motor (filled bars) and somatosensory (open bars) cortices described by four different measures of movement representations. (*A*) Total activated cortical volume per movement. (*B*) Primary cluster volume relative to total activated volume per movement. (*C*) Number of non-contiguous clusters constituting each movement representation. (*D*) Pairwise overlaps of movement representations (cortical volume shared by both movements as a percentage of volume activated by either movement). Horizontal axis refers to individual movements (Little/LIT, little finger flexion–extension; Sequence/SEQ, sequential finger opposition; Thumb/THU, thumb flexion–extension; Wrist/WRI, wrist flexion–extension). Data are shown as group means ± SEM.

of data did not allow statistically significant somatotopy to be found.

Volume and Spatial Distribution of Activation in M1 and S1

The average volume of activated M1 and S1 increased in the order Little Thumb Wrist Sequence, where all pairwise differences except that between Little and Thumb were significant. S1 volumes were slightly but not significantly larger that those of M1 (Fig. 3*A*).

Each movement activated several non-contiguous foci in M1 as well as S1 (Fig. 3*B*,*C*). However, repeated measures ANOVAs with movement as the within variable and cluster count and relative size of the primary cluster as dependent variables in M1 and S1 determined that the spatial distribution of active cortex was significantly different for M1 and S1.

Overall, there were significantly more clusters of active cortex in S1 than M1 (4.7 ± 2.4 versus 2.9 ± 1.4; P = 0.0023, paired t-test) and the primary S1 cluster accounted for a significantly smaller fraction of total active cortical volume (S1, 63 ± 22%; M1, 78 ± 17%; P = 0.016, paired t-test). In M1, movement type had no statistically significant effect on the number of clusters [$F(3,30)$ = 0.5; P = 0.67] or the primary cluster [$F(3,30)$ = 0.4; P = 0.35]. In S1 there was a significant main effect of movement type on number of clusters [$F(3,30)$ = 5.4; P = 0.0047], where active cortex representing Sequence and Thumb was distributed into significantly more clusters than Little (P = 0.05, Student–Neuman–Keuls) while the main effect of movement on the relative size of the primary cluster was not significant [$F(3,27)$ = 2.5; P = 0.085].

Extent of M1 and S1 Hand Representations

Measuring the area activated with any finger movement (Thumb, Little or Sequence) provided an estimate of the size of the sampled hand representation. In M1 the distance between most distant points was 47 ± 10 mm, while in S1 it was 49 ± 11 mm. The difference between M1 and S1 within subject was not significant (P > 0.6, paired t-test).

Other Cortical Areas in Simple and Sequential Movements

We have also observed activation of higher motor and somatosensory areas, similar to other functional imaging studies (Roland and Zilles, 1996; Fink *et al.*, 1997). These areas were consistently active during sequential movement but also significantly active during simple movements in most subjects, even though the volumes of active cortices were much smaller during simple movements than during sequential movements. Activation in the non-primary sensorimotor system involving ipsilateral M1, premotor cortex, supplementary motor area and cingulate motor area was less consistent in amount and localization and no somatotopy was established in these areas.

Discussion

Our study demonstrates the presence of a 3-D somatotopic gradient in the primary somatosensory and motor cortices (S1 and M1) of the human. At the same time, the representation of each movement was distributed into multiple non-contiguous foci (clusters) and representations of different movements were not segregated into discrete areas but showed significant overlap. The significance of COM separation was high in the medial–lateral (x) and anterior–posterior (y) directions in both M1 and S1. In the inferior–superior (z) direction the centroids were significantly separable in S1 but only approached significance in M1, which we attribute to the lower spatial resolution in that (through-plane) direction.

Representation of movements in S1 was similar to M1 but more discrete, as will be discussed in more detail below.

Principal M1 Concepts: Somatotopy and Overlaps

Somatotopy has been the dominant feature of most historical accounts of the arrangement of human M1 (Hughlings Jackson, 1863; Foerster, 1936a; Penfield and Boldrey, 1937). These early studies uncovered the presence of an orderly representation of body parts along the precentral and postcentral gyri, where the head sub-division is located most ventrally and laterally near the lateral sulcus, hand and arm dorsal to the head and trunk and leg most superiorly and extending onto the medial surface of the hemisphere. Furthermore, an orderly arrangement was also found within the hand, where thumb was found most laterally and little finger most medially (Penfield and Boldrey, 1937).

Further evidence for separable representation of fingers comes from studies of cortical injury. Although lesions to M1 have generally produced distributed motor deficits, those relatively rare lesions that are small enough and localized enough to be confined to the precentral gyrus (e.g. small ischemic strokes and gunshot wounds) have been found to cause focal paralyses; the deficits can be limited to a few fingers or even to specific movements of a single finger, leaving other movements and fingers intact (Foerster, 1909, 1936a; Schieber, 1999).

Complementary to somatotopy, the distributed and overlapping character of the motor representation was not ignored by early investigators of the motor cortex, but since that time this fact has been occasionally understated. According to Hughlings Jackson a single part of the body is represented 'preponderatingly' in one part of the human precentral gyrus, but it is also represented in other parts of the gyrus, even though to a different degree and in different combinations with other body parts (Hughlings Jackson, 1931). Foerster observed that from a single precentral locus repeated surface stimulation can evoke a series of different movements of individual fingers, which was interpreted as meaning that each point contains neurons representing different body parts (Foerster, 1936a). Finally, Penfield and Boldrey showed clear overlap of sites where stimulation evoked movements of different fingers in their figures 12 and 13, although these findings are not discussed in the text (Penfield and Boldrey, 1937). In the present study, as well as in Penfield and Boldrey, wrist sites have been found lateral to thumb sites and vice versa.

Unfortunately, textbook reproductions of Penfield's (Penfield and Rasmussen, 1950) homunculus, which are presented without mention of the complex data behind it, may have given the false impression of segregated, non-overlapping somatotopy in M1 [even though the authors themselves warned against this oversimplified interpretation (Penfield and Rasmussen, 1950)]. This fact may be partly responsible for the emphasis in more recent studies on the overlapping nature of the human and monkey M1 maps. Consequently, somatotopic arrangement and distributed character have sometimes been treated as mutually exclusive features of the primary motor representation.

Until recently, more detailed examination of the M1 organization was only possible in non-human primates. There, mapping studies of M1 have used electrical intracortical microstimulation with improved spatial resolution [for reviews see Asanuma, Humphrey and Lemon (Asanuma, 1989; Humphrey, 1986; Lemon, 1990)] and consistently confirmed the existence of spatial segregation of the major sub-divisions (head, arm, trunk and leg) of the M1 map. However, some intracortical stimulation studies in monkey M1 have reported a completely fragmented mosaic pattern of muscle representations within the arm representation, with no apparent somatotopy (Kwan *et al.*, 1978; Gould *et al.*, 1986; Donoghue *et al.*, 1992). Unfortunately, most intracortical stimulation mapping studies use a single threshold to elicit movements at each cortical site, thus obscuring the more contiguous and overlapping character of movement representations (Humphrey, 1986).

The distributed character of M1 hand representation and sharing of neural substrate by different movements have also been demonstrated with single neuron recordings in the monkey during trained movements of individual fingers, where single neurons participated in movements of different fingers, while the presence of relative somatotopy was not consistent (Schieber

and Hibbard, 1993). The anatomical properties of the primate corticospinal tract, both convergence (Phillips, 1969) and divergence (Fetz and Cheney, 1980; Shinoda *et al.*, 1981), were suggested to be the anatomical substrate contributing to the overlapping and distributed muscle representations.

Recently, non-invasive imaging and mapping methods have been used to study somatotopy within the human M1 hand representation. Unlike stimulation studies, these methods can map cortical areas participating in natural voluntary movements. Using a blood flow-sensitive MRI technique, Sanes *et al.* showed a distributed and overlapping representation of finger movements in M1, without clear somatotopy (Sanes *et al.*, 1995). On the other hand, Kleinschmidt *et al.*, like the present study, used high-resolution blood oxygenation level-dependent mapping and found limited evidence suggesting relative somatotopy by direct comparisons between different movements in a single slice through M1 (Kleinschmidt *et al.*, 1997). Absolute somatotopy (contrasting different movements with rest) was hard or impossible to discern (Kleinschmidt *et al.*, 1997). The present study did find absolute somatotopy in the group results, possibly owing to the benefit of having obtained multi-slice data through most of the hand representation. The individual arrangement was still quite variable.

The discrepancy between Sanes *et al.* (Sanes *et al.*, 1995) on the one hand and the present study and that of Kleinschmidt *et al.* (Kleinschmidt *et al.*, 1997) on the other, could be caused by lower spatial resolution of the former and by a difference in the source of functional imaging contrast (flow versus BOLD). However, locations of peak cortical blood flow changes during movement of different parts of the arm might be separable even with low resolution maping (Grafton *et al.*, 1993). Such results can be explained by the presence of two overlapping and opposing cortical gradients within the hand representation, as suggested by Schieber (Schieber, 1999). Nevertheless, on the basis of the current data we cannot exclude the possibility that representations of movements of individual fingers have distinct centroids, as suggested by human cortical lesion studies (Foerster, 1909, 1936a) and cortical stimulation studies (Foerster, 1936a; Penfield and Boldrey, 1937).

Complementary to somatotopy, the present study confirms the presence of distributed multi-focal representation (Sanes *et al.*, 1995) and the amount of M1 overlap found in the present study compares very well with previous fMRI studies (Sanes *et al.*, 1995; Kleinschmidt *et al.*, 1997). The individual features of distributed M1 movement representations will be further discussed below. The location of thumb movement representation agrees with previous data; a thumb movement dipole was previously found 39 ± 11 mm from the midline (Gerloff *et al.*, 1998), while our distance was 34 ± 4 mm, albeit in the non-dominant hemisphere, which may have a smaller hand representation (Volkmann *et al.*, 1998).

S1 Somatotopy

Although the S1 activation in the present study can be attributed to direct motor input (efferent copy) and to somatosensory input (resulting mainly from proprioception), the demonstrated S1 somatotopy is similar to that previously shown during skin stimulation with MEG (Hari *et al.*, 1993; Nakamura *et al.*, 1998), SSEP (Buchner *et al.*, 1995) and fMRI (Maldjian *et al.*, 1999). Similar to Maldjian *et al.*, we found consistent somatotopy, and, in agreement with their study (Maldjian *et al.*, 1999), the group results were more conclusive than the rather variable individual somatotopy. The distance between the S1 thumb and little finger centroids was smaller in our study (3.2 ± 1.6 versus 18 mm) but direct comparison is difficult since Maldjian *et al.* (Maldjian *et al.*, 1999) used vibratory stimulation in contrast to the presumed proprioceptive processing in this study. Also, their distance is derived from Talairach-transformed group data, while ours is based on individual anatomies.

If we were able to analyze the S1 sub-areas separately, the somatotopy observed in the current study may have been even clearer because the hand representation in 3a/3b would be expected to have more discrete somatotopy than that of area 1, which itself has greater somatotopy than area 2 (Iwamura, 1998). Unfortunately, there are no clear gross anatomical landmarks to separate the S1 sub-areas (Geyer *et al.*, 1999).

The location of thumb movement representation in S1 agrees with previous data; a dipole related to thumb movement was found 41 ± 8 mm from the midline (Gerloff *et al.*, 1998), while our distance was 38 ± 4 mm. In agreement with Gerloff *et al.*, the S1 thumb centroid is located more laterally than the corresponding M1 centroid (Gerloff *et al.*, 1998).

Extent of M1 Hand Representation and Somatotopic Separation of Movements

Despite being limited to a 30 mm thick section of M1 and S1 for technical reasons, the area covered should be representative of the M1 hand representation, the average vertical extent of which (across slices) was found to be 30.4 ± 5.6 mm (Sanes *et al.*, 1995). Penfield and Boldrey mention that fingers could be stimulated from an area extending 55 mm along the central sulcus (single case) (Penfield and Boldrey, 1937); in our study the Euclidean distance of the extreme ends of the area activated with any finger movement was of the same order (46 ± 10 mm). Volkmann found the maximum distance between the (non-somatotopically organized) dipole sources of different finger and wrist movements to be 9.4 ± 3.5 mm, while their magnetoencephalographic data did not allow for direct measurement of the whole extent of the hand representation (Volkmann, 1998).

Schieber and Hibbard recorded M1 neuronal activity during monkey voluntary movements and found the extent of macaque hand representation to be 8–9 mm (Schieber and Hibbard, 1993). In one monkey, where somatotopic ordering of firing frequency centroids was found, separation of the centroids was much smaller than the extent of the hand representation (2 compared with 9 mm) (Schieber and Hibbard, 1993). Our study also found the centroid separation to be small, 2.5 ± 2.0 mm (comparable with the voxel size), while the extent of mapped hand representations was 47 ± 10 mm. It is important to note, though, that the centroid of firing frequency used by Schieber and Hibbard (Schieber and Hibbard, 1993) may not be directly comparable to the COMs reported here because our weighting by correlation coefficient is only indirectly related to synaptic turnover and neuronal firing. The fact that the cortical distances presented here are very conservative, since they are linear distances rather than full traces of the winding course of M1 around the hand representation knob, is also possibly important for these comparisons.

Individual Variations: Genetics and Experience

Part of the variability of COM coordinates can be attributed to the variable size and topography of the cerebral cortex of individual subjects. We did not try to remove this variability (e.g. by transformation into a standard coordinate system) because it would lead to loss of anatomical information and it was not necessary to do so since all comparisons were within subject.

Although some of the individual variability in the order of movement COMs can be explained by the uncertainty introduced by the experimental method, it is also likely to represent true biological variability. We speculate that the observed arrangement of movement is a result of common genetic predisposition for orderly somatotopy that has been modified by individual experience (Nudo *et al.*, 1992, 1996). That is why we chose to examine the non-dominant hand, where the hand behavioral experience should be less diverse across subjects, leading to less variable cortical movement representations. An analogous situation exists in the primary visual cortex, where innate orientation specificity maps can be modified but not completely overridden by experience (Sengpiel *et al.*, 1998).

Volume by Movement in M1 and S1

M1 and S1 differed when the volume of activated cortex was compared between simple movements and the sequential movement. In M1 using the three finger sequence activated only about twice the cortical volume of the single finger movements (this difference was not significant). In S1 it was about three times larger, i.e. proportional to the number of fingers used (this difference was significant).

Although our S1 volumes were larger than those of Gelnar *et al.* (Gelnar *et al.*, 1998), our volumes of activated M1 cortex were smaller than previously published (Karni *et al.*, 1995; Sanes *et al.*, 1995). This could be explained in part by the greater spatial resolution and the resulting greater spatial specificity of the present study, but could also reflect lower sensitivity of the present study due to a lower signal-to-noise ratio associated with higher spatial resolution at medium magnetic field strength. In that case, our overlaps are likely to be somewhat underestimated. Nevertheless, most of our results are not likely to be affected by these absolute volumes because we compared movements with each other and/or M1 with S1. [Use of a higher statistical threshold $r = 0.4$ ($P < 0.01$) does not significantly change the results presented here.] Lastly, our definition of the anterior limit of the M1 region may have been more conservative than those used by Karni *et al.* and Sanes *et al.* (Karni *et al.*, 1995; Sanes *et al.*, 1995).

Spatial Complexity Analysis in M1 and S1

Distribution of M1 activation into multiple clusters has been reported before (Sanes *et al.*, 1995) and the number of clusters observed agrees with the present study. In our study both M1 and S1 showed a multifocal pattern of activation, although active S1 cortex was distributed into more non-contiguous foci than M1 and less of the activation was concentrated in the largest cluster (Fig. 3*B*,*C*). This could result from the fact that primate S1 is composed of four sub-areas (3a, 3b, 1 and 2) and at least two of them, 3a and 2, are expected to participate in the proprioceptive processing that our tasks required (Kaas, 1990; Iwamura, 1998). Areas 3a and 2 are located on opposite ends of S1 and the corresponding activation should show up as discontinuous. Anatomical sub-areas were also found in M1 [4a/4p (Geyer *et al.*, 1996)], but they lie next to each other and their active cortex is more likely to have fused into one region in this study.

The sequence task, a sequential multi-finger movement, activated more separate S1 foci than single finger and wrist movements, while there were no significant differences among movements in M1. There is a line of parallel evidence in the non-human primate cortical mapping literature: orderly and relatively discrete somatotopy was found in several sub-regions of S1 (Kaas *et al.*, 1979; McKenna *et al.*, 1982), while evidence from M1 was either against somatotopy in general or supported a non-discrete overlapping somatotopy, where the centers of mass lie in the somatotopic order but each location in M1 can be associated with different hand muscles/movements (Foerster, 1936a; Schieber and Hibbard, 1993).

Proprioceptive processing of the sequential movement in S1, on the other hand, should reflect the multiplicity of different body parts and manifest a more pronounced multifocality for the three finger sequence. Discrete somatotopy in S1 allows for additive activation, such that the three finger movement cortical volume is the sum of the volumes for the individual fingers moved alone. This does not seem to be the case in M1, where the 'sum of the parts' is qualitatively different than the sum found for S1.

These differences between M1 and S1 in the discreteness of internal somatotopy of activation complement the above mentioned differences in volume of active cortex, together suggesting that M1 and S1 share a common somatotopic principle but that the somatotopy in S1 is more discrete and segregated, in contrast to the more integrated and overlapping somatotopy in M1.

In conclusion, our study supports the presence of a 3-D somatotopic gradient in the human M1 and S1 hand representations. On the other hand, movements are not segregated into discrete areas and activation with different hand movements overlaps, more significantly in M1 than in S1. This reaffirms the historical conception based on clinical observations and electrical stimulation in epilepsy patients (Foerster, 1936b; Penfield and Boldrey, 1937) and recently confirmed by electrophysiological recordings in non-human primates (Schieber and Hibbard, 1993) that motor representations in M1 form distributed networks. Importantly, we also confirm the other conclusion of these authors that the existence of such a distributed organization does not in itself argue against the presence of a somatotopic gradient and, in fact, that it is very likely that the two exist side by side in a complementary fashion.

Finally, this study supports previous findings of both the similarities and differences in M1 and S1. The results suggest that while M1 organization is mostly distributed and overlapping, with a non-discrete somatotopic gradient, S1 organization shows a clearer more segregated somatotopy and multiple foci of activation, possibly correlating with different cytoarchitectonic sub-divisions of S1.

Notes

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