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Functional Variability of the Human Cortical Motor Map: Electrical Stimulation Findings in Perirolandic Epilepsy Surgery

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Summary: The purpose of this study was to assess the cortical representation of sensorimotor functions in patients undergoing perirolandic epilepsy surgery, focusing on somatotopy, mosaicism, and variability of function in relation to the classic motor homunculus. The authors studied 36 patients in whom intraoperative or extraoperative electrical cortical stimulation to map motor functions was performed. A computer program was devised to register electrode number, stimulation parameters, and response to each stimulus. Electrode position was represented graphically whenever a stimulus was delivered. A total of 43 maps from 36 patients were analyzed. The authors found variations in the organization of M1 (primary motor cortex) in seven patients (19.4%). Four patients (11.1%) presented mosaicism (overlapping of functional areas), two (5.6%) presented variability (inverted disposition of M1 functional areas), and one (2.8%) had both. The results of this study challenge the notion of orderly topographic relationships between the human sensorimotor functions and their representation in the primary motor cortex. These results confirm those of other studies with animals and humans using novel imaging techniques, suggesting that the motor homunculus may not always be considered a definite and absolute representation of M1. **Key Words:** Brain mapping—Motor cortex—Motor homunculus—Somatotopy.

Localizing the cortical sites of motor and cognitive functions has been a challenge for scientists throughout history. Penfield and Boldrey (1937) postulated the existence of a correlation between human body parts and their representation on the cerebral cortex. In 1937 they proposed a pictorial representative plan for the localization of motor and cognitive functions in the brain, a humanlike figure—the homunculus (Penfield and Boldrey, 1937). Later, this first homunculus was drawn over a section of cerebral cortex, thus refining the relationship between the primary motor and somatosensory areas in the brain and the various parts of the human body (Penfield and Rasmussen, 1952). This was called *somatotopy*.

Although both the homunculus and somatotopy were developed further (Penfield and Jasper, 1954), the somatotopic representation of the human motor and sensory cortices as neatly organized arrangements in which each part of the body is controlled from a specific, discrete cortical site is still accepted. However, recent work has challenged this traditional view by pointing out that the

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distribution of sensorimotor functional areas in the cerebral cortex may vary in several ways (Barinaga, 1995; Branco et al., 1996). For instance, a study with monkeys (simius) showed that the representative areas for different fingers in the primary motor cortex (M1) are organized as an overlapping mosaic of several neuronal populations that control the movement of each finger with variable degrees of specificity, in the manner of a gradient of anatomic–functional representation (Schieber and Hibbard, 1993). This contradicts the classic view that each finger of the hand is represented independently lateromedially on M1, from the thumb to the little finger, and controlled uniquely by a strict subset of neurons. In fact, these areas seem to form a continuum in which each finger cannot be individualized easily (Schieber and Hibbard, 1993). Further data have demonstrated that the cortical representation of sensorimotor functions in humans may be altered as a result of their motor or sensory activities; for example, string players might develop a bigger sensory area for the fingers than nonmusicians (Elbert et al., 1995).

Currently, several research efforts are addressing the issue of cortical representation of motor and sensory functions. All have produced data demonstrating variability (in relation to somatotopy) and overlap of M1 functional areas. One of these initiatives is the neurophysiologic study of animals to investigate the inner structure of the motor cortex, its connections, and how this organization determines the elaborate control of the several muscles involved in each movement (Donoghue et al., 1992; Schieber and Hibbard, 1993). Another field of research involves the study of the motor regions in normal subjects (humans without cerebral pathologic processes) using functional image mappings such as functional MRI (Kleinschmidt et al., 1997) and positron emission tomography (Colebatch et al., 1991; Grafton et al., 1991; Kim et al., 1993; Rao et al., 1995).

A third field relates to clinical practice and aims at obtaining information about M1 and other motor areas through electrical or magnetic stimulation mapping in epileptic patients undergoing surgery. These stimulation procedures are part of the presurgical and intraoperative evaluation of patients undergoing perirolandic epilepsy surgery. Therefore, the main goal of the current study was to assess the organization of M1 in these patients, and to compare this organization with a traditional, somatotopic model.

METHODS

We studied 36 patients with partial epilepsy and medically refractory seizures who underwent presurgical evaluation for perirolandic epilepsy. They all had multiple video-EEG recordings to evaluate ictal and interictal epileptiform activity, 1.5-T MRI studies, neuropsychological evaluation, and, occasionally, ictal single photon emission computed tomographic imaging. Based on the results of these diagnostic studies, the most likely epileptogenic zone in these patients was localized in perirolandic regions. This localization prompted the need for a detailed functional mapping of the sensorimotor cortex by electrical stimulation, to plan the extent and boundaries of the cortical tissue to be resected.

We collected data on age at surgery, age at onset of the epilepsy, gender, frequency, duration, and etiology of the epilepsy, lateralization of the epileptic focus, abnormalities on neurologic examination, and MRI findings.

Electrical stimulation procedures were intraoperative in 11 patients, extraoperative in 22, and both procedures were performed in three patients. Extraoperative stimulation was used for patients who were unable to undergo craniotomy under local anesthesia, or for those in whom subdural electrodes were implanted to delineate better the epileptogenic zone. When feasible, extraoperative stimulation was complemented by intraoperative stimulation, thus allowing a more precise anatomic definition of the motor map.

All stimuli consisted of biphasic square wave pulses with a duration of 0.3 msec/phase, a frequency of 50 Hz, and trains lasting from 2 to 5 seconds, delivered from a Grass S12 constant current stimulator or from a Grass S48G voltage stimulator coupled to an SIU5 stimuli isolation unit. Current intensity started at 1.5 mA and was increased gradually to a maximum of 15 mA or to a level producing after-discharges. When the Grass S48G was used, the applied voltage and the current delivered with each stimulus were monitored using a Tektronix digital storage oscilloscope. Several authors have demonstrated the safety of these parameters, which do not cause electrolytic lesions in the cerebral cortex (Da Costa et al., 1998; Ojemann, 1996; Schott, 1993). The current was kept constant with variations not superior to 20%, thus avoiding responses to different thresholds. Maximal stimulation intensity depended on the sensory or motor response or the occurrence of after-discharges during the electrocorticographic monitoring.

Intraoperative stimulation was delivered across 1-mm silver ball bipolar electrodes, 5 mm apart. All evoked responses were rechecked to ensure that they were reproducible. Intraoperative stimulation was used when the surgical procedure required only a brief and not an extremely detailed mapping process (well-defined epileptogenic area). The motor responses analyzed were

TABLE 1. *Patients with mosaicism or variability*

Patient no.	Type of stimulation	Pathology	Response evoked
1	Intraoperative	Frontal posttraumatic gliosis	Flexion of the left hand and flexion of the forearm at the same point (overlapping/mosaicism)
2	Extraoperative	No apparent pathology	Paresthesia of fingers and deviation of the tongue and angle of the mouth at the same point (overlapping/mosaicism)
3	Extraoperative	No apparent pathology	Numbness and flexion of the left shoulder at the same point (overlapping/mosaicism)
4	Extraoperative	No apparent pathology	Flexion of the fingers and deviation of the angle of the mouth at adjacent points (overlapping/mosaicism) Inversion of finger and face representations in relation to the homunculus (variability)
5	Extraoperative	Polymicrogyria	Movement of the tongue and flexion of the right hand at the same point (overlapping/mosaicism)
6	Intraoperative	Focal cortical dysplasia	Alteration of wrist and finger representations in relation to somatotopic representation (variability)
7	Intraoperative	Tumor	Alteration of thumb and mouth representations in relation to somatotopic representation (variability)

elicited from patients who were either awake or unconscious.

Extraoperative cortical electrical stimuli were applied using subdural electrodes of 2.5 mm in diameter (interelectrode distance, 10 mm). The electrodes (platinum or stainless steel) were mounted on a 32-electrode Silastic plate or on an eight-electrode strip (Ad-Tech Medical Instrument Corporation, Racine, WI) implanted through a craniotomy over the area to be mapped (Da Costa et al., 2000). Each patient underwent several sessions of electrical stimulation over 2 to 4 days. The electrode selected as reference was an inactive contact on the subdural grid, which was electrically silent on initial stimulation. Other reference electrodes were used randomly to confirm that the responses elicited from a particular electrode were reproducible and that they did not result from stimulation of a given cortical area between two electrodes. Afterward, we performed a sequence of stimuli that started at one of the corners of the plate or strip, each stimulus being applied through a pair of adjacent electrodes, one active and one used as reference. When a response was achieved, other surrounding electrodes were used as a reference to confirm the finding. Responses elicited were rechecked several times on at least two different days to ensure their reproducibility.

A computer program was devised to store data and to plot the position of the electrodes on standard images of the human brain or on digitized neuroimages from the actual patients. The program ensured the reliability of our data analysis because it automated the registration of electrode number, stimulation parameters (amperage, voltage, and impedance values), stimulus duration, and patient response to each stimulus. In addition, the position of the electrodes was represented on a brain image whenever a stimulus was delivered. Only responses obtained from stimuli applied to M1 were taken into consideration (Table 1).

We looked for two different aspects of M1 organization that have been previously addressed by Schieber and Hibbard (1993) : mosaicism (overlap) and variability. Mosaicism is the representation of more than one body part on a limited cerebral area. It may also be interpreted as the control of different parts or muscles of the body by a single region with single neurons, as well as the control of different body parts by small independent areas that are highly overlapping. In turn, variability is defined as two or more areas of representation in the brain, which differ from the motor homunculus in terms of spatial arrangement.

Stimuli responses were categorized based on the following criteria: To characterize *mosaicism* or overlap, we considered that the M1 functional areas for different parts of the body overlapped when two or more motor responses from distinct parts of the body were elicited on stimulation of the same cortical point or of immediately adjacent points (against what was originally proposed by Penfield and Boldrey [1937]). Specifically, we considered as overlapping those areas that, on stimulation of the same or immediately adjacent cortical points, elicited combined motor responses from somewhat distant parts of the body (for instance, finger and mouth). For the purposes of this study, we did not consider as overlap the coexistence of responses for movements of closely associated cortical regions, such as the fingers and the hands, because that could hardly be seen as unexpected.

To fall under the category of *variability*, responses had

TABLE 2. *General characterization of patients*

Variable	All patients, %	Patients with variations on M1, %
Gender		
Male	44.44	42.85
Female	55.56	57.14
Epilepsy classification		
Simple partial	19.44	14.28
Complex partial	44.44	28.57
Partial with secondary generalization	13.89	0
Generalized	8.33	28.57
Ignored	11.11	14.28
Nonepileptic patient	2.78	14.28
Age of epilepsy onset, y		
0–15	82.85	100
16–20	2.86	0
21–30	2.86	0
31–40	8.57	0
>40	2.86	0
Frequency of seizures		
1–3/mo	8.57	0
1–5/w	48.57	50
6–10/w	11.43	16.67
11–20/w	5.71	0
21–30/w	11.43	33.33
30–40/w	2.86	0
>40/w	11.43	0
Duration of epilepsy, y		
0–10	28.57	0
11–20	45.71	33.33
21–30	20	50
>30	5.71	16.67
Age at surgery, y		
0–15	17.14	0
16–20	8.57	0
21–30	28.57	50
31–40	34.28	33.33
>40	11.43	16.66
Laterality		
Right	42.86	50
Left	48.57	33.33
Ignored	8.57	16.67
Neurologic examination		
Normal	72.97	85.71
Hemiparesia	8.10	0
Facial palsy	5.40	0
Mental retardation without focal deficits	5.40	0
Global bradikynesia without focal deficits	2.78	14.29

to be distributed spatially on M1 in a conformation that clearly deviated from that originally postulated by Penfield's motor homunculus—namely, when a nonsomatotopic distribution of two or more motor responses was seen. Therefore, nonsomatotopic motor distribution was considered as variable in relation to the classic motor homunculus (for instance, inversion of the finger and face regions—in other words, face above the finger).

To be considered as a valid case, variability or mosaicism had to occur at the minimum level of current necessary to cause a motor response, minimizing confusion with spread of current to other areas. We excluded from the analysis findings suggestive of mosaicism and variability for which the responses were not rechecked or for which we were uncertain of the exact electrode position. Electrical stimulation findings were analyzed further in relation to clinical and neuroimaging features to define eventual correlates of variability and mosaicism (Table 2). Contingency tables were used to compare these features in the group of patients with and without variations of M1 organization.

The study protocol was approved by the ethics committee at Hospital São Lucas, Pontificia Universidade Católica do Rio Grande do Sul, Brazil.

TABLE 2. *Continued*

Variable	All patients, %	Patients with variations on M1, %
Global hyperreflexia with positive Hoffman and Babinski bilaterally	2.78	0
Left dysdiadochokinesia	2.78	0
NMR*		
Expansive lesion	17.07	14.29
Calcified lesion	2.44	0
Gliosis	9.75	14.29
Scar	2.44	0
Cortical dysplasia	4.88	14.29
Polymicrogyria	2.44	14.29
Hippocampus atrophy	14.63	0
Hypersignal in hippocampus	2.44	0
Hypersignal in T2 in hippocampus	14.63	0
Asymmetry between lateral ventricles	2.44	0
Unspecific alterations	4.88	0
No alterations	17.07	42.86
Ignored	4.88	0
Anatomopathologic results		
Hippocampal sclerosis	13.88	0
Cortical dysplasia	19.44	28.57
Gliosis	8.33	14.29
Vascular congestion	8.33	0
Ischemic alterations	2.78	0
Hemorrhage	5.55	0
Tumor	25	14.29
Glioma	2.78	0
Astrocytoma	11.11	14.29
Cavernous angioma	2.78	0
Oligodendroglioma	2.78	0
Glioblastoma	2.78	0
Ganglioma	2.78	0
No alterations	2.78	0
Ignored	13.88	42.86

* Some patients presented more than one alteration on MRI. NMR, nuclear magnetic resonance.

RESULTS

A total of 43 human motor cortical maps based on cortical electrical stimulation of 36 patients were analyzed. Of the 43 maps, there were 19 (44.2%) intraoperative and 24 (55.8%) extraoperative. Motor responses were obtained in 24 maps (55.8%), which were considered for the study of M1. Throughout the study we also obtained sensory responses in 14 of 24 extraoperative mappings (58.3%).

Following the criteria described earlier, we found variations of M1 (variability or mosaicism) in seven patients (19.4%). Four (11.1%) presented mosaicism, two (5.6%) presented variability, and one had both (2.8%; see Table 1). Among the seven patients with variations in M1, four had extraoperative stimulation procedures. A pathologic diagnosis for epilepsy was not achievable in three patients and the other four had, respectively, a frontal posttraumatic gliosis, a polymicrogyria, a cortical dysplasia with balloon cells, and a low-grade glioma (see Table 1).

In patient no. 1, stimulation of a same point resulted in simultaneous flexion of the hand and flexion of the forearm, suggesting mosaicism of the cortical areas responsible for hand and forearm movements. Similarly, patient no. 5 presented movement of the tongue and flexion of the right hand on stimulation of the same point. Patient nos. 2 and 3 presented an unexpected kind of mosaicism, involving sensory and motor areas. In patient no. 2, stimulation of the same point evoked paresthesia of fingers and deviation of the tongue and the angle of the mouth, showing that besides functional overlap (sensory and motor) there was also overlap of different body regions (mouth and fingers). In patient no. 3 there was simultaneous numbness and movement of the left shoulder in response to stimulation of a single point, again showing overlap of different functions (motor and sensory). Patient no. 4 presented both variability and overlap, with a horizontal orientation of the region in which flexion of the fingers and deviation of the angle of the

mouth occurred. Mosaicism also seemed evident because the distance between the different response sites is only 1 cm. In the case of patient nos. 6 and 7, there was variability with an inversion in the position of the fingers and of the wrist (patient no. 6), as well as of the thumb and of the mouth (patient no. 7). In patient no. 6 we found a representative region for the fingers above the wrist region, and in patient no. 7 the mouth was represented above the thumb (Fig. 1).

Table 2 compares clinical and imaging features of the complete group and the subgroup of seven patients with variations in the organization of M1. We did not observe any difference between these groups that could be related to the findings of variability and mosaicism.

There were two cases of meningeal irritation without infection (5.6% of the total patients), three patients had asymptomatic subdural hematoma (8.3%), and in one patient the electrode plate deviated from the original position (2.8%).

DISCUSSION

According to Colebatch et al. (1991), normal subjects may display an overlapping distribution of M1 functional regions. In fact, since the first appearance of the homunculus (Penfield and Boldrey, 1937), data obtained from neurophysiologic studies on monkeys (Donoghue et al., 1992; Schieber and Hibbard, 1993; Schieber and Poliakov, 1998) or with noninvasive, functional imaging techniques in humans (Colebatch et al., 1991; Grafton et al., 1991; Kim et al., 1993; Rao et al., 1995) support the hypothesis of functional mosaicism of motor cortical regions (Sanes et al., 1995). We have found mosaicism involving the sensorimotor regions related to the hand, the arm, the lips, and the tongue, as well as variability in the spatial cortical representation of the fingers, the wrist, the thumb, and the mouth. In one patient (patient no. 4) presenting simultaneous flexion of the fingers and deviation of the angle of the mouth, the observed regional orientation was horizontal, whereas a vertical orientation is predicted by the classic homunculus. In the same patient, the distance between the different response sites was 1 cm, which is less than what is expected according to the homunculus, thus suggesting mosaicism.

The actual frequency of mosaicism or variability was probably underestimated in our study because we excluded from the analysis those patients with mosaicism and variability for whom we were unable to define precisely the electrode positions or for whom the elicited responses were not rechecked. In addition, the cortical region investigated was restricted to areas surrounding the possible epileptogenic zone, because we did not carry out unnecessary stimuli in other regions (besides those required for the presurgical routine of these patients). Our most frequent finding was mosaicism, which is similar to what was reported in other studies with nonhuman primates (Donoghue et al., 1992; Schieber and Hibbard, 1993).

Why mosaicism occurs is still open to speculation. It could be that, rather than the discrete control implied by the classic somatotopic maps, motor and cognitive functions requiring coordinated neural processing for some motor actions are mediated by overlapping representations (Sanes et al., 1995). In the current study, patients had refractory epilepsy with or without structural damage, and thus our findings should not be extrapolated prematurely to persons without either epilepsy or damage around the central regions of the cortex. In fact, we speculate that our results could be related to either the preexisting pathology, to the chronic epileptiform activity, or to both, because these may interfere with the normal cortical organization, indicating plasticity of M1. However, Penfield's homunculus was depicted from stimuli performed in the same kind of patients studied here. Thus, we think our findings suggest that the classic homunculus has failed to incorporate the actual potential to mosaicism and variability within the primary motor cortex. It is not our intention to propose a new homunculus or a new overlapping map, but rather to point out the existing potential for variations in the organization of M1.

Indeed, experimental and clinical observations suggest that the cortex is capable of reorganization after cortical lesions (Hedström et al., 1992; Ramachandran et al., 1992), specific training (Recanzone et al., 1992), or lesions of peripheral motor nerves (Cohen et al., 1991; Merzemich et al., 1983). The growth of intracortical connections could account for much of the cortical reorganizations of the sensory area (Florence et al., 1998). For instance, after long-term denervations of upper lines in macaque monkeys, the representation of the face in somatosensory cortex expands over the representation of the hand as a result of a functional expansion of this representation in the thalamic nucleus (Jones and Pons, 1998; Pons et al., 1991).

Among our patients with variations of the homunculus, only one had abnormalities on physical examination (global bradykinesia without focal deficits). Thus, we suggest that the variations in M1 do not, per se, cause clinically detectable motor abnormalities. Also, the normal motor examination in six of seven patients with mosaicism or variability suggest that the influence of structural lesions or epileptiform activity around the

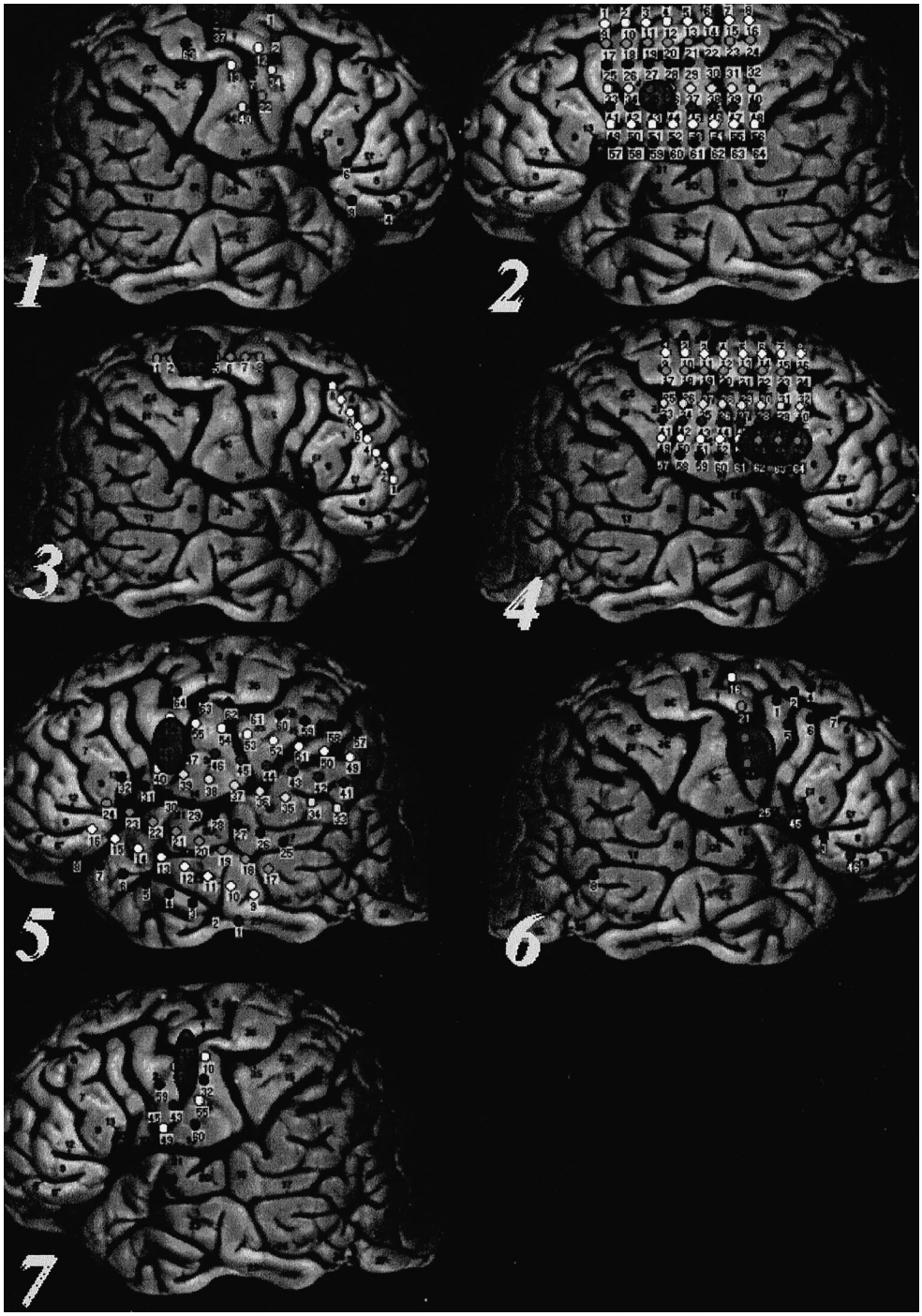

FIG. 1. The image reveals the mapping for the 7 patients with mosaicism and variability. The dark ellipse indicates where the variation in the organization of Ml was seen.

motor area may not have been a major determinant of these variations.

Indeed, some experimental findings and evidence from our series strongly suggest that this phenomenon may be generalized to normal human beings, at least to some extent. These include the fact that mosaic patterns are observed in nonepileptic and nonlesioned primates studied by electrical stimulation (Schieber

and Hibbard, 1993), and also that no alterations were found in our other 29 epileptic patients, many of whom also had perirolandic lesions. In addition, three of our patients presented M1 somatotopic variations without any structural pathology that could justify such variations. Even artificial modeling of M1 has produced findings that are compatible with mosaicism through the use of artificial neural network computation for simulation of overlapping motor engrams (Lukashin et al., 1994). If our observations are confirmed, classic teaching and theories concerning the somatotopic organization of the sensorimotor cortex should be revised.

We think that the most important aspect to be stressed in the current work is that by using the same kind of technique used by Penfield in the 1950s, we were able to show that M1 is not as precisely organized and compartmentalized as it appears to be in neurophysiology textbooks. Penfield's homunculus is said to be an exact representation of M1, without any mention of the possible variations discussed in this paper (e.g., see Kandel et al. [2000]). It is possible that some of our results might be explained by some technical variations. For instance, 56% of our motor maps were built from extraoperative stimulation, which allows more precise localization of function. Indeed, four of the seven patients with variations were studied by extraoperative stimuli. Another potentially important detail is that we used amperage as the control variable for stimulus intensity, whereas Penfield and colleagues used voltage, which can be related to different levels of electrical current, and depends on the impedance of the underlying tissue. Despite the fact that Penfield himself established the homunculus as a pictorial simplification of M1 for mnemonic purposes only, it has been considered a very good approximation of reality. Our results, however, suggest that this simplification is superficial, and this concept has also been advanced elsewhere (Morris, 2002). At least it is becoming more clear that the homunculus is an approximation for a *functional* distribution of motor areas, rather than an *anatomic* distribution that correlates every discrete body part to a certain discrete M1 subregion. To determine to what extent it is an adequate functional representation, more studies are needed. Because ethics prevent the performance of electrical stimulation studies in normal individuals, we expect that the development of more accurate, noninvasive, brain mapping techniques may some day enable a better understanding of the relationship between body parts and their functional representation in the brain.

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