Functional architecture of the motor homunculus detected by electrostimulation

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Key points

- We performed a prospective electrostimulation study of the motor homunculus in 100 patients without motor deficit or brain lesion in the precentral gyrus in order to acquire accurate MNI coordinates of the functional areas.

- The analysis of 248 body coordinates in the precentral gyrus showed rare inter-individual variations in the medial-to-lateral somatotopic movement organization with quite similar intensity thresholds. Electrostimulation only induced basic and stereotyped movements.

- We detected a relative medial-to-lateral somatotopy of the wrist/hand/global/individual fingers, with sometimes different sites for an individual muscle or movement.

- We found some similarities to but also substantial differences from the seminal work of Penfield and colleagues.

- We propose an updated version of the human motor homunculus and of its correlation with the somatosensory homunculus, previously defined in MNI space with a similar brain mapping technique.

Abstract

In this prospective electrostimulation study, based on 100 operated patients without motor deficit or brain lesion in the precentral gyrus, we acquired coordinates of the functional areas of the motor homunculus and normalized them to standard MNI space. Among 608 sites stimulated in the precentral gyrus (and 1937 in gyri nearby), 248 positive points (40%) for motor response were detected—245 in the precentral gyrus. Positive stimulations were detected through the “on/off” outbreak effect, and only basic movements were detected. We found no significant difference in mean intensity threshold between the motor representations of the fingers (1.94 mA), tongue and

lower limbs (both 2.0 mA), or face (2.25 mA). In the precentral gyrus, the evoked body movements displayed a medial-to-lateral somatotopy in very small (often <10 mm^2) areas. The hand region displayed multiple areas for a specific movement, with areas inducing either global or single finger movement (with a relative medial-to-lateral somatotopy). Among these tested patients, the somatotopic organization of the intact motor cortex showed little inter-individual variations. Unlike Penfield and collaborators, we evoked no sensations such as sense of movement or desire to move, and only 2% of motor responses outside the precentral gyrus. We propose a rationalization of the standard drawing of the motor homunculus according to MNI space. We found a somatotopic correlation perpendicular to the central sulcus when matching our motor data to those previously obtained for the somatosensory homunculus.

Key words: Homunculus, Electrical stimulation, Motor systems

Professor Franck-Emmanuel Roux is a neurosurgeon specializing in the treatment of patients with brain tumors. For more than 20 years, his primary research focus has been brain mapping during awake surgery. Publications of his team at the University Hospital of Toulouse have involved the fields of language and sensorimotor systems or right hemispheric attentional systems. He has been particularly interested in handwriting, exploring the relationship between language and motor systems. He has also participated in more than 30 humanitarian surgical missions, especially in Cambodia, where he has provided pediatric neurosurgical treatment and trained local surgeons on a long-term basis.

Introduction

The primary motor cortex can be divided into 2 distinct cytoarchitectonic areas named Brodmann Areas (BAs) 4 and 6 (Brodmann, 1909; Vogt & Vogt, 1919), with BA 4 being the main area of the precentral gyrus. The most obvious cytoarchitectonic feature of the primary motor cortex in human and non-human primates (Von Bonin & Bailey, 1947) is the presence of large Betz cells in layer V. The anterior limit between BA 4 and BA 6 is matter of debate, but BA 6 encompasses mostly the base and anterior part of the precentral gyrus (White *et al.*, 1997). Some animal studies have shown that BA 4 could be organized somatotopically with relatively sharp boundaries between body parts (Dum and Strick, 2002). Nevertheless, this somatotopy could be relative, with stimulation of spatially separated sites activating the same muscle and stimulation of single sites activating more than one muscle (Huang *et al.,* 1998, Donoghue *et al.*, 1992), and has even been questioned (Graziano *et al.*, 2005) The arrangement of multiple sites for individual muscles or movements would allow single muscles to be engaged in multiple synergies with other muscles for various movements (Schieber, 2001). Furthermore, the superior limb somatotopy could not be organized on a medial-to-lateral pattern (Schieber and Hibbard, 1993) but rather was configured as a central core for distal limb movements surrounded by proximal limb movement sites (Kwan, MacKay, Murphy, & Wong, 1978 ; Park, Belhaj-Saïf, Gordon, & Cheney, 2001 ; Graziano, Taylor, Moore, & Cooke, 2002). Studies of the output of corticomotor neurons demonstrated that they could directly influence several muscles (Shinoda *et al.*, 1981), with the possibility, according to the activation threshold level, that small clusters of neurons activating a single muscle (Asanuma & Rosen, 1972).

In humans, most of our knowledge emanates from activation studies (Kleinschmidt &Toni, 2005) or magnetic stimulation (Metman *et al.*, 1993), because in contrast to stimulation of other brain regions, intracortical stimulations (in epileptic patients for instance) of the precentral gyrus are limited by the risks of possible (often irreversible) damage. Among the rare invasive studies of the primary motor cortex, Penfield and his co-workers (Penfield & Rasmussen, 1950; Penfield & Jasper, 1954) mostly described the functional anatomy of motor area, emphasizing the somatotopic organization of the hemibody. More recently, some activation studies have also found a somatotopic organization of the somatomotor hemibody (Dechent & Frahm, 2003), although other studies challenged this view (Sanes *et al.,* 1995) with, for instance, a different somatotopy for the index finger—lateral to rather than medial to the thumb area (Lotze *et al.*, 2000). Many studies underline the functional (Metman *et al.*, 1993, Branco *et al.*, 2003) and/or anatomical (White et al., 1997)

variability of primary motor maps and their possible reorganizations after brain injuries (Stoeckel *et al.*, 2009, Roux *et al.,* 2000).

Since the seminal works of Penfield and colleagues, no systematic mapping of the human primary cortex has been performed in a large number of awake operated subjects. Moreover, these previous studies involved patients with impaired (and possibly reorganized) precentral gyri. The present work was a prospective electrostimulation study based on 100 intact patients (i.e., patients with no motor deficit and no lesion in the precentral gyrus). The aims of this investigation were to acquire accurate coordinates of the functional areas of the motor homunculus in the standard MNI space and to study the human superior limb in particular. Parameters of excitability of human primary motor areas in conscious individuals are also discussed.

Material and methods

Ethical approval

The National Consultative Committee of INSERM (Institut National de la Santé et de la Recherche Médicale) gave its approval for the storage of patients' data and preservation of their anonymity (approval no. 2007-32). To preserve patient privacy, this study was not registered in a publicly accessible database. However, the study conformed to the standards set by the Declaration of Helsinki. All the patients and their families gave informed consent for a study of the functional areas by direct brain mapping and each chart was discussed pre-operatively in a surgical staff meeting with different neurosurgeons. Once 100 brain mappings had been included, the study was closed.

Inclusion criteria

Data from successive awake surgery brain mappings were prospectively collected by the same team using the same protocol throughout the 14 years of the study (February 2005–September 2019). For purposes of this study, patients were considered neurologically intact with respect to motor function if they had no demonstrable motor deficit based on testing or if they claimed that they had no deficit but testing revealed a very slight, clinically insignificant, deficit. In order to be included in the study,

patients had to meet this criterion and have no brain lesion directly located within the precentral gyrus.

Patients were examined with respect to absence of preoperative motor deficit using clinical tests. Before the surgery, each patient claiming that she/he had no motor deficit underwent 3 tests: the Motricity Index, the Nine-Hole Peg Test, and assessment with the House-Brackmann grading system (to exclude patients with any sign of facial palsy).

In summary, the Motricity Index provided a rating of the power and range of active movement for the upper (shoulder abduction, elbow flexion, and pinch between the thumb and index finger) and lower (hip flexion, knee extension, dorsiflexion) limbs (Demeurisse *et al.,* 1980). The minimum score is 0 and the maximum 100. We considered patients with a score > 95/100 for the side contralateral to the affected hemisphere.

The Nine-Hole Peg Test is a test of manual dexterity (Sharpless, 1982). The patient is asked to pick up nine dowels from a tray at table height and place them as quickly as possible into nine holes in a neighbouring horizontal board within a time limit of 50 s for each trial. Three trials were given with each hand, alternating between the side ipsilateral to the affected hemisphere and the contralateral side. Results are expressed as number of pegs placed per second. The mean for test completion in normal people is 18 s (Sharpless, 1982). We excluded patients who took more than 30 s to complete the test with the hand contralateral to their brain lesion. Finally, the House-Brackmann scale grades the degree of facial paralysis; grade I is assigned to normal function, and grade VI represents complete paralysis (House & Brackmann, 1985).

Overall, all patients had a Motricity Index score of 100 for the side contralateral to their brain lesion. The mean Nine-Hole Peg Test score in our cohort was 17.33 s in the hand ipsilateral to the brain lesion and 18.24 s in the contralateral hand (this difference was not significant; t-test, $P = 0.296$, 95% CI −0.8042 to 2.6242). All patients had a House-Brackmann score of I (normal).

The selection and the inclusion of the patients with no deficit was one of the most difficult parts of this study and the reason why it spanned 14 years. The main scientific advantage of this approach was to allow us to obtain data presumed close to normal functional anatomy. The drawback was that because our ability to test the human brain was constrained by clinical requirements, the number of stimulations we could deliver and the areas we could stimulate were limited. We tested only what was actually useful for the treatment of the patients. Stimulation far from detected positive areas (areas in which stimulation induced movement) may not have been performed

because such testing was not clinically relevant for the patient. This legitimate constraint limited the ability to find complete somatotopies of the part of the body tested in individual patients.

Exclusion criteria

Other criteria for exclusion were: patients operated on under general anaesthesia with or without deficit and a brain lesion within or near the precentral gyrus, patients under 18 years of age, and patients operated on using awake surgery but with brain lesions within or close to the precentral gyrus andor motor deficit.

Pathology treated

Electrostimulation for brain mapping was performed to help with the removal of recently discovered brain lesions. The mean time between the first clinical sign and operation was 20.55 days (range 7–50 days; SD 9 days). We found 28 (28%) WHO grade I and II gliomas, 44 (44%) WHO grade III and IV gliomas, 8 (8%) arteriovenous malformations or cavernomas, 17 (17%) metastases, 2 (2%) grade II meningiomas. In 64 cases the lesions were located in the right hemisphere, and in 36 cases in the left. The mean age of the patients was 46 years (range 18–81 years, SD 15 years), and 41 of the patients were women; 96 were right-handed (Oldfield, 1971). Overall, 76 (76%) patients had been recently treated with antiepileptic drugs, always less than 3 months before the operation. None of them had chronic intractable epilepsy.

Anaesthetic protocol for awake craniotomy

Our awake brain mapping protocol was based on 20 years' experience (Roux *et al.*, 2017). Anaesthetic drugs can, in theory, interfere with stimulation thresholds. Our objective during brain mapping was to avoid any anaesthetic drugs. One hour before admission to the operating room, a patch containing a eutectic mixture of prilocaine (2.5 mg/g) and lidocaine (2.5 mg/g) (EMLA) was applied in the supraorbital and auriculotemporal regions. Lidocaine 1% with epinephrine 1:100,000 was infiltrated to block the supraorbital, auriculotemporal, and occipital nerves. Additionally, the Mayfield head holder (Ohio Medical, Cincinnati, OH, USA) pin site and the surgical skin incision line were infiltrated. Sedation with spontaneous respiration was provided by continuous infusion of propofol (1–3

mg/kg/h). Fentanyl (1–3 μg/kg/h) or remifentanil (0.01–0.25 μg/kg/h) was used for analgesia. The depth of procedural sedation was adjusted to maintain stability of the patient's vital signs. Propofol infusion was stopped during the dural opening (around 10 min before brain mapping) and the patient was fully awakened. Once the cortical mapping procedure was completed, the patient was put back to sleep using the same protocol for the rest of the operation.

Cortical procedures

A neuronavigational system was used to guide all tumour removals. Anatomical structures (gyri and sulci) were identified according to the neuronavigational data and the visual identification of the shape of gyri and sulci. The cortex was directly stimulated before any surgical approach using the bipolar electrode of the Nimbus cortical stimulator (1 mm electrodes; Innopsys, Toulouse, France) with biphasic square wave pulses of 1 ms duration (each phase 0.5 ms) and 50 Hz trains. The maximum train duration of each stimulation was 3 s.

Only clear brain mapping data were included in this study. Patients' feedback was fundamental: we considered that a response was obtained when the patients acknowledged feeling something (e.g., muscle contraction) or the team detected a movement. Patients were encouraged to report their movements during stimulation. No electromyographic recording was used in order to avoid additional discomfort for the patients as well as additional technical issues in this already demanding procedure.

The patient's level of alertness in the absence of stimulation was regularly evaluated throughout the testing as further assurance that changes during stimulation were not random events. Non-reproducible positive responses to electrostimulation were not included in this study. As in our recent study of the reproducibility of language trials in brain mapping (Roux *et al.*, 2019), we used a reproducibility criterion. In the present study, the initial criterion was 2/2 (i.e., 2 positive responses in 2 stimulations would validate a cortical site as "positive"). When only 1 of the 2 initial simulations produced a positive response, we stimulated the site at least one more time: sites with 2 positive responses out of 3 positive stimulations were considered to satisfy the reproducibility criterion but those with only 1 positive response were not.

To evaluate the current amplitude for motor mappings in precentral gyri, stimulation was first applied at 1 mA and progressively increased by 0.5 mA increments (maximal intensity: 6mA). If

patients felt an unpleasant or painful motor sensation, or any movement that could be interpreted as possible seizure activity, we stopped the stimulation and then started again at a lower intensity.

The presupposition of this study in terms of localization was that, as described in other human anatomical, activation, or receptor-binding studies (White et al., 1997), BA 4 is bordered posteriorly by the central sulcus and occupies mostly the precentral gyrus. In its lateral aspect, this gyrus is also composed of BA 6, which lies farther away from the Rolandic fissure and corresponds to the ventral and dorsal premotor areas described in non-human primates (Dum & Strick, 2002). Since a part of BA 4 is buried in the central sulcus and not accessible to electrostimulation, the current functional exploration focuses on the crown of BA 4 and BA 6. In their work, Penfield and Rasmussen claimed (on the basis of 15 patients in whom "the banks of the Rolandic fissure were stimulated below the outer or superficial surface") that the motor responses they obtained from the surface of the precentral gyrus were comparable to those obtained from the immediate zone located deeper in the Rolandic fissure (Penfield & Rasmussen, 1950).

In our 100 patients, 608 sites were stimulated overall on the precentral gyrus and 2545 in neighbouring gyri (**Table 1**). When a functional site was found, it was marked by a sterile ticket of 0.25 mm^2, identified in neuronavigation before moving on to the next test site. It was decided that the minimum spatial resolution of our electrostimulation technique corresponded to the size of the bipolar electrode separated by 3 mm. When a positive site was found, we stimulated the nearby cortical areas to validate its spatial resolution and make sure that no other responsive response was detected close to it.

Postoperative data analysis

Each patient had her/his positive stimulations positioned on the left or right 3D cortical surface reconstructions of one of the individual brains (case 12) constituting the PALS (population-average, landmark- and surface-based) atlas (Van Essen, 2005) provided in the Caret software (Van Essen et al., 2001) and normalized in the MNI space. We obtained normalized coordinates of stimulation site locations that were per-operatively visualized and positioned on original 3D images provided by the neuronavigation software (Brain Lab). For each positive site, MNI space coordinates (X, Y, Z) were obtained and stored in an Excel database, with intraoperative photographs and detailed accounts of the evoked responses. Note that the localizations of unresponsive cortical areas were registered according to their gyral localizations but not using MNI coordinates.

Results

Among 608 sites stimulated in primary motor cortex, we found 248 areas that were positive for movement (40.78%). The motor positive areas were located in very small patches of cortex (approximately 3 mm x 3 mm - Fig. 1).

Types of induced motor responses

Types of movements detected are detailed in Table 2. The movements were *stereotyped* (i.e., repeated stimulation on the same area induced the same movement, whatever the initial position of the limb) and *basic* (for instance, finger flexion or extension, tongue contraction). Flexions of the digits and wrist were evoked much more often than extensions. The velocity of the movement was high and did not follow the profile of a normal movement. We did not detect complex movements with stimulation of the primary motor cortex (for instance, no movement mimicking the act of bringing food to the mouth). No vocalization was observed. Induced movements were contralateral to stimulation except in 35 cases of tongue contraction, 13 cases of lip contraction, and possibly in 14 cases of larynx paralysis. In the larynx cases, we were unable to detected whether the induced muscle contractions were uni- or bilateral. No other sensations from the proprioception domain (such as "desire to move" or "movement imagination") were detected. Rarely, isolated movements were found when stimulations were performed outside the precentral gyrus (3 times over 1937 points of stimulations).

The general motor contralateral body homunculus

Figure 2A shows the somatotopic sequence of the human body with MNI coordinates along the left and right precentral gyri of our template brain. Each symbol represents a positive stimulation site, and the colour code indicates the body part from which a movement was evoked. Various movements of the feet, knee, hip, eyebrows, jaws, tongue, and larynx were detected in BA 4, forming well-defined clusters with little inter-individual variability. All MNI coordinates of body positive points are presented in Tables 3 and 4. These tables confirm that the variations in localization were limited. The total length of the precentral gyrus (top/down over the sylvian fissure)

on the template used was 11.2 cm for the left hemisphere and 13.8 cm for the right). The standard deviations of main individual areas (inferior limb, individual and all fingers, shoulder, elbow, wrist, larynx) calculated from MNI coordinates, were all less than 6 mm. Localizations were slightly more variable for the face, lips, and tongue areas, a rather large region in the motor homunculus. However, even in this region, the standard deviation for each body part was less than 7 mm for the X and Y coordinates and less than 14 mm for the Z coordinate (superior/inferior axis). Figure 2B shows the rostro-caudal repartition of the motor areas within the precentral gyrus. Overall, and for most body parts, positive stimulation sites were quite well centered with respect to the crown of the precentral gyrus, with very few positive sites beyond 5 mm from it. The lowest panel of Figure 2B shows that the centering of positive sites with respect to the crown of the precentral gyrus is also independent of the low (0.5 mA) to high (5 mA) intensity threshold.

Parameters of stimulation

Stimulation of motor primary areas had several characteristics (intensity threshold; type of outbreak; accuracy). The mean general intensity threshold was 2.1 mA (range 0.5–5 mA) with a limited standard deviation (SD 0.9 mA), as shown in Fig. 2C. A single threshold was used in 88 cases. But in 12 cases, we used 2 or 3 different thresholds to induce movements of different body parts (e.g., 2 mA for the hand and 2.5 mA for the elbow). Evoked movements begin suddenly with the onset of the stimulation and then stop at the cessation of the stimulation (on/off outbreak effect). Group analysis showed no difference between intensity thresholds of different body parts (Kruskal Wallis test; $\chi^2(7,240) = .12.90$; p-value = 0.07). Patients who were taking antiepileptic drugs (n=76) and those who were not (n=24) did not differ in intensity thresholds (2.38±1.03 mA and 2.23±0.75 mA respectively; Wilcoxon rank sum test; z-value =0.43; p-value = 0.66).. Additionally, older patients (>=60 years old; n = 26) and younger ones (<60 years old; n = 74) did not differ either in intensity thresholds (2.52±0.99 mA and 2.29±0.96 mA respectively; Wilcoxon rank sum test; z-value =0.93; p-value = 0.35) Positive stimulations were detected with a clear-cut “threshold” effect (for instance, a movement evoked at 2 mA but not at 1.5 mA). Pain was felt only five times by one patient because of limb contraction and the stimulation was stopped. Epilepsy induced by stimulation was detected in 12 patients, always resolved upon irrigation of the cortex with cold Ringer’s lactate solution.

The specific motor hand and face homunculus

Hand and wrist responses were found in 51 patients with a relative somatotopy, i.e., from medial to lateral part of the gyrus, we found sites for the elbow, wrist, and then hand (areas controlling digit movement). Individualized digit movements were detected preferentially (but not exclusively) in the lateral-most part of the hand region. Thumb flexion areas (opposition movements) were by far the most common (accounting for 50% of the total single finger movements) among other areas controlling individualized finger movements. Several areas could be involved in a single finger movement irrespective of their specificity (i.e., for instance, flexion of the index finger could be induced by a specific area or by a distinct area that also induced flexion of one or more other fingers). Thumb movement areas were mostly located laterally to other finger areas, but they were also surrounded by global or individual finger flexion areas. Considering the individual level of analysis, we detected individual movements of the thumb and at least one individual movement of another digit in only 3 patients (patients 1, 56, and 57; see Table 3B for details). A medial-to-lateral somatotopy (the thumb on the lateral part and the other digits oriented one by one more medially) was only detected in one of them (patient 56). Analyzing data from not only these 3 specific patients but the whole group of isolated-digit MNI coordinates we could not detect a clear medial-to-lateral somatotopy. Figure 3A suggests the existence of 3 clusters for the fingers (The mean values for X coordinates were calculated based on absolute values): 1) a medial cluster for flexion or extension of the wrist (mean X coordinate : 26); 2) a central cluster that activates “all fingers” (mean X coordinate : 32); 3) a lateral cluster for individual fingers without clear somatotopy (mean X coordinate : 35). In summary, taking together the individual and group level analysis, wrist, all fingers, and individual fingers (thumb and other fingers) could be the medial-to-lateral somatotopic sequence of the hand.

Cortical sites evoking movements of the face (including tongue) were found over a large part of the precentral gyrus in 52 patients (blue symbols in Fig. 2A). As shown in Fig. 3B, they also presented a medial-to-lateral somatotopic sequence from the forehead to the larynx muscles, passing through

the eyes and lips/tongue areas, directly related to the somatosensory somatotopicsequence found in the postcentral gyrus (Roux *et al.*, 2018). In group analysis, areas of the tongue and lip movements were intermingled (Fig. 3B). Nevertheless, individual analysis of the 11 cases in which both lip and tongue movements were evoked indicated a clear medial-to-lateral sequence for upper lip, lower lip, and tongue, in that order.

The left/right differences and the somatosensory/motor concordance

Computing the relative medial (0) to lateral (1) location of the stimulation sites along the precentral gyrus in both left and right hemispheres reveals little inter-hemispheric variability in their somatotopic organisation. As shown in Fig. 4, this organisation also shows a striking concordance with that of the somatosensory homunculus along the postcentral gyrus, which we recently investigated with a similar approach (Roux et al., 2018).

Table 5 shows that the somatotopy is largely preserved across the left and right hemispheres and across the sensory and motor domains. We performed a 3-way analysis of variance (ANOVA) with the normalized distances as dependent variables. The 3 factors were the somatotopy (body part representations), the laterality (left/right hemisphere), and the domain (sensory/motor). We used eta-squared (η^2) measures to evaluate the percentage of variance explained by each factor and by their interactions. If the somatotopy is relatively well preserved across the hemispheres and across the motor and sensory domains, most of the variability should be accounted for by the somatotopic distribution of the stimulation sites. Actually, it is what we observe. The full 3 factors model accounts for 73.7% of the variance in positive sites locations, demonstrating a low inter-individual variability Crucially, the somatotopy alone explain 71.3% of the variance while, by comparison, the other 2 factors (laterality and domain) account for only 0.0% and 0.5% of the variance, respectively.

Discussion

Our direct electrostimulation analysis of the human precentral gyrus (primary motor cortex) reveals a consistent and relatively fine-grained medial-to-lateral somatotopic organisation. What are the main points of this somatotopy?

First, the contralateral movements of the body are represented in small patches of cortex. Cortical stimulation of a small patch of primary motor cortex resulted in a fixed signal on a muscle or a group of muscles inducing *isolated movements* (e.g., selective flexion of a single finger, raising of the contralateral eyebrow, or extension of several fingers). Movements were also *stereotyped* (i.e., repeated stimulation induced the same movement) and *basic* (i.e., we did not detect complex movements, such as digital manipulating types of movements, such as in closing the buttons of a shirt, or reaching the hand to the mouth). This finding suggests that stimulated neurons of the primary motor cortex represent specific movements or groups of agonist muscles involved in a movement. Sometimes the accuracy of the electrostimulation allowed stimulation of neurons controlling the specific fibres of a muscle inducing for instance an isolated index finger flexion (i.e., activation of some fibres of the flexor digitorum profundus controlling the tendon to the index finger)—or in the case of isolated dilatation of the nostrils, a group of neurons controlling the contralateral dilator naris. With our type of stimulation, we did not detect complex movements in response to stimulation of the primary motor cortex (or the premotor cortex) as described in primates (Graziano *et al.*, 2005). These more elaborate movements are not induced *but are inhibited* by electrostimulation of premotor cortex (BA 6) or its underlying white matter. This phenomenon has been demonstrated in humans for various types of elementary movements (Luders *et al.*, 1995; Rech *et al.,* 2019) and for specific movements of writing (Roux *et al.,* 2009).

Second, we find in the human precentral gyrus (in these intact patients) a rather orderly organized map of the contralateral body. Some electrostimulation studies in human (Penfield & Rasmussen, 1950) or in primates (Graziano *et al.*, 2005) and activation (Meier *et al.*, 2008) or cytoarchitectonic (Rademacher, 2001) studies have argued for a certain variability of this motor functional organization or even questioned the somatotopy of the precentral gyrus (Graziano, Taylor, & Moore, 2002). The main question concerns what is considered as "variability" in a functional organization or even the definition of "somatotopy". Our results revealed very little aberrant somatotopic organization, and the localization of each cortical representation of movement within the precentral gyrus showed a high degree of consistency (the standard deviations of the barycentres of main "cortical" representations were minimal), matching the definition of somatotopy—"point-for-point

correspondence of an area of the body to a specific cortical point". Our results are in line with data acquired through sub-millimeter fMRI signal analysis, showing that cortical areas for individual digits are arranged in a column-like fashion and differentially engaged in different motor actions (Huber *et al.*, 2020). This somatotopy echoes the clinical findings that limited lesions of the precentral gyrus cause focused paralysis of specific body parts (Foerster, 1936; Celebisoy *et al.*, 2007). Cytoarchitectonic studies have shown interindividual variations in the organisation of BA 4 but a good interhemipsheric organisational consistency at the level of individual subjects (Rademacher, 2001). We detected that individual movements could be induced by multiples sites, in line with previous observations in monkeys (Schieber, 2001). Nevertheless, our findings of a relative lateral-to-medial somatotopy of the hand area do not match the findings of those who denied a somatotopic organisation of the motor cortex (Graziano, Taylor, & Moore., 2002; Schieber & Hibbard LS, 1993).

Thirdly, although we detected many types of movements of the contralateral body, two main zones were detected: the hand and the face/tongue. The hand and the face/mouth areas occupied parts of the cortex that were proportionally much larger than their body volume. The human cortical representation of the tongue occupies an area at least as large as that of the hand. The relatively high number of positive responses found for hand and face/tongue is an indirect sign that the human brain has multiple cortical representations of some muscles, increasing the human abilities of these two body regions. Our medial-to-lateral somatotopy of the human hand motor function is relative but seems slightly more organised than what has been found in some primate studies (Schieber & Hibbard LS, 1993). The reasons could be methodological, human patients being able to localize specifics of the movement (through self report). Nevertheless, most of the movements analyzed in our study were detected by the surgery team rather than by the patients themselves. Are the reasons due to differences across the species? This could be speculative but, although many non-human primates have opposable thumbs, the human thumb is longer and more mobile. The finding of many individual thumb motor areas (in comparison with areas for other fingers) could be related to the central role of the thumb in humans.

Finally, this somatotopy of the primary motor cortex matched that of the primary somatosensory cortex in most regions. Comparisons of the MNI coordinates of the somatosensory topographies in the postcentral gyrus (Roux *et al.,* 2018) and of the induced movements of the contralateral body in the primary motor were organized perpendicularly relative to the central sulcus.

Human primary motor cortex positive thresholds

In patients with an intact precentral gyrus, motor responses were obtained with mean intensity thresholds around 2 mA for the tongue, hand areas, or lower limb and with slight individual variations. These positive threshold levels were lower than those identified for other parts of the human brain, notably those measured in the somatosensory cortex (Roux et al., 2018) or in language-related areas (Roux *et al.,* 2017; Ojemann *et al.*, 1989). Slightly higher motor thresholds (around 3 mA) have also been found during extraoperative stimulations in conscious patients (Kovac *et al.*, 2011). In patients operated on under general anaesthesia, motor thresholds are much higher (Simon *et al.*, 2010); Suess *et al.* (2006) reported motor thresholds over 10mA. In our study, neither the age of our adult patients nor treatment with antiepileptic drugs had an effect on these thresholds. Positive thresholds could be modified by a variety of confounding factors (Haglund *et al*., 1993), such as current frequencies and monopolar versus bipolar stimulation devices, the type of anaesthesia used, stimulations during the refractory period, the presence of a motor deficit, or maybe patients' skills, and these possibilities remain to be investigated.

As for the somatosensory cortex (Roux *et al.*, 2018), 59% of patches of primary motor cortex were unresponsive to stimulation (i.e., the patient had no visible movements and did not report any muscle contraction). It is a common in human electrostimulation brain studies to find areas not responsive to stimulation (Penfield & Rasmussen, 1950; Branco *et al.*, 2003). The reasons could be multifactorial and not exclusive. First, contrary to a common belief that electrostimulation of the precentral gyrus activates movement, stimulation may actually inhibit movement in some parts of this structure (i.e., "negative" motor areas), as shown in premotor areas (Luders *et al.*, 1995). To detect this phenomenon, we would need to change our testing protocol and ask patients not to be passive but to perform movements during stimulation. Furthermore, fearing induced seizures or current diffusion by horizontal axonal branching to sites other than the stimulated ones, once the positive current threshold found, in general we did not try to raise current intensity too much. Some neurons could be induced by higher current (Boroojerdi *et al.*, 1999)—i.e., the activation threshold of some muscles in the precentral gyrus could be different. In this study, we found that it in some patients we needed 2 or 3 different but close thresholds to activate different movements. Finally, some muscle contractions not perceived by the patients could have been detected by electromyography, which we did not use. Thus, clinical information (and further scientific data) could thus have been missed.

Differences from the findings of Penfield and colleagues

Although our study matches many of the findings of Penfield and co-workers, 3 main differences can be noted.

First, Penfield and colleagues found that "around 20% of the motor responses" were outside the precentral gyrus, particularly in the postcentral gyrus (Penfield & Jasper, 1954; Penfield & Rasmussen, 1950), for almost all parts of the human body but especially for the hand, lips and jaw. This lack of "clear cut" distribution of the motor responses was in line with their description of somato*sensory* responses in the *pre*central gyrus (Penfield & Jasper, 1954; Penfield & Rasmussen, 1950) but in contradiction to Sherrington's seminal electrostimulation works on primates, which showed no motor responses in the postcentral gyrus (Sherrington, 1906). In our series, although it was possible to find motor responses outside the precentral gyrus, this finding was very rare (3 sites out of 1937). We hypothesized that the accuracy of the stimulator we used, in terms of localization (with 3-mm–wide electrodes) and stability of its electrical frequency (in contrast to the stimulators used by Penfield and colleagues), allowed us to better control the electrical stimulations we used and avoid their diffusions. Another hypothesis is that paradoxical responses may not have been uncommon in the epileptic patients treated by Penfield, particularly in those with organic lesions and chronic epilepsy (Urasaki *et al.*, 1994). Some of Penfield's patients had also huge brain lesions around the central gyri and thus may have had cerebral reorganization. Finally, the current intensity we used could have been too low. Although some direct connections exist between the premotor cortex and the spinal cord (Rech *et al.*, 2019), these pathways were rarely activated by the current intensity we used. Also, in this study we did not stimulate the supplementary motor area, a cortical zone where electrocortical induced movements can be detected (Penfield & Jasper, 1954; Penfield & Rasmussen, 1950).

Second, Penfield's team described some movement-related sensations produced by stimulation, including a sense of movement and, more rarely, a desire to move (Penfield & Jasper, 1954; Penfield & Rasmussen, 1950). They also described a large zone in the precentral gyrus including the lips, jaw, and tongue areas where in patients stimulation produced "vocalization" (a loud and sudden sound), salivation, or even automatic mastication. None of these responses were evoked by electrostimulation of the intact precentral gyrus in our patients. Finally, Penfield and Rasmussen noted that "the great majority of the responses in man were located adjacent to the central fissure" (Penfield & Rasmussen, 1950). Our findings showed that motor responses were obtained from the

whole surface of the precentral gyrus (especially in its more medial parts) and not only from the part close to the central fissure.

Limitations

Since no EMG responses were collected, the responses were determined subjectively by the patient or experimenters in most cases. We cannot exclude that isolated movements could have been accompanied by unnoticed but more widespread and complex responses of smaller magnitude. This report bias might also explain the gap in responsive units between the face and the hand areas, possibly related to unnoticed responses in neck muscles or hand/mouth complex micro-responses.

Data availability

All raw data are included in the paper (table 3, 4 and 5).

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Experiments were performed at The University of Toulouse III. FER was responsible for the study design. FER and MN carried out the experiments. FER, MN, SC, and JBD analysed and interpreted the data. FER, CG, and JBD drafted the paper. All authors revised the article critically for important intellectual content. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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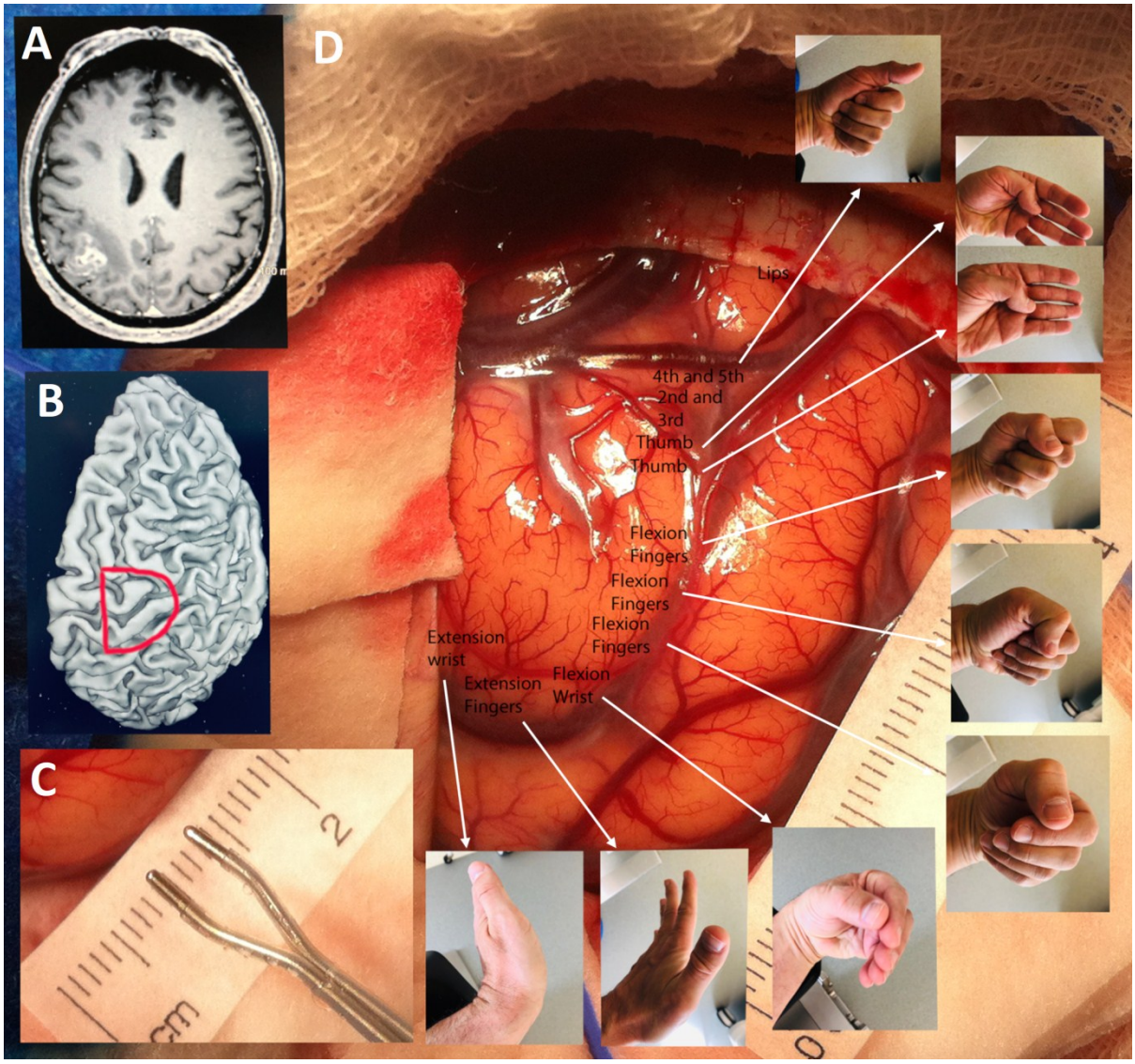

Figure 1. Example of electrostimulation mapping for precentral gryus: results obtained in a 59-year-old man with a right grade IV astrocytoma and no sensorimotor deficit

A: Axial T1 image showing a right grade IV astrocytoma (WHO 2016). **B:** 3D image of the right hemisphere, showing the location of the bone flap (outlined in red). **C**: Electrode tips, showing the 3-mm distance. **D:** In the precentral gyrus (BA 4), electrostimulation showed clear wrist, finger, and lip movement somatotopy, in small (3-mm wide), sharply delimited cortical areas as follows: **wrist** (MNI coordinates: X = 27.3, Y = −25.2, Z = 70.2), and **finger extensions** (29.6, −25.7, 69.1); **wrist** (32.9, −24.6, 67.4) and **3 areas of all-finger flexions** (34.9, −24.1, 65.6; 36.0, −22.3, 65.6; 35.7, −19.9, 65.6); **2 areas of thumb flexion** (35.5, −15.7, 66.1; 34.9, −13.8, 66.2); and areas of **flexion of the 2nd, 3rd, 4th and 5th fingers** (34.4, −10.9, 64.6). The illustrative photographs are of the patient's hand. Laterally, an area of **superior lip contraction** was detected (41.7, −6.6, 57.6). We observed that the displacement of the bipolar electrode on the cortex located adjacent to a positive area often induced another movement. The finding of individual or grouped finger areas lateral to the thumb area was not infrequent in our group of patients.

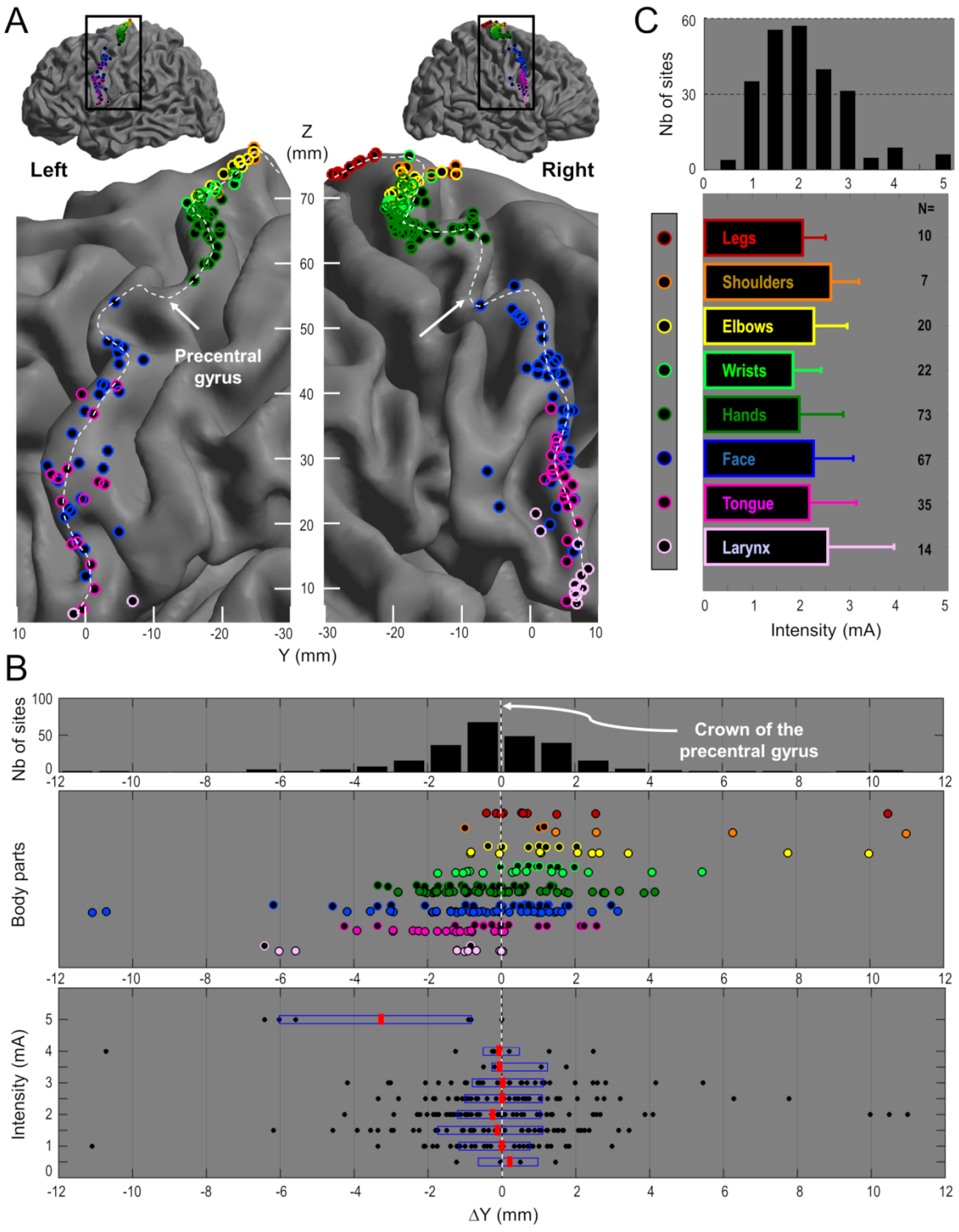

Figure 2. The motor somatotopy sequence of the human body and intensity thresholds

A: Distribution of the motor representation of contralateral hemibody over the left and right hemispheres of the template brain. The medial to lateral sequence of motor responses includes the legs (red), shoulders (orange), elbows (yellow), wrists (pale green), hands (dark green), face (blue),

tongue (purple) and larynx (pink), with a dominance of responses from the face and hands. **B**: The upper panel shows the antero-posterior location of the stimulation sites relative to the crown of the precentral gyrus ("delta" Y, in mm). Negative values stand for posterior locations, toward the central (rolandic) fissure. Symbols with black centers and solid-coloured symbols stand for stimulation sites in the left and right hemispheres, respectively. (Same colour code as in Fig. 2A.) The middle panel shows the localizations of the motor areas were rather equally distributed along the crown of the precentral gyrus, face and tongue areas being preferentially located more posteriorly, close to the central fissure. The inferior and superior limbs are more distributed along the gyrus. This repartition encompasses mostly BA 4. The lowest panel indicates that positive sites with low to high intensity thresholds remain well centered with respect to the crown of the precentral gyrus. **C**: The upper panel shows the overall distribution of intensity thresholds, ranging between 0.5 and 5 mA, with a mean of 2.10 mA (SD 0.90 mA). The lower panel shows the mean intensity thresholds (with error bars indicating SDs) for the different body parts in this series of intact patients varying around 2 mA: finger (1.94 mA, range 1–2.5 mA, SD 0.92), tongue (2.02 mA, range 1.5–2.37 mA, SD 0.91), lower limb (2 mA, range 1.5–2.50 mA, SD 0.81), face (cheek or nose contractions, eyebrow movements) intensity thresholds (mean intensity 2.25 mA, range 2–2.50 mA, SD 0.492). Intensity thresholds do not vary significantly between these motor representations (Kruskal-Wallis test, $\chi^2 = 12.90$, $P = 0.07$).

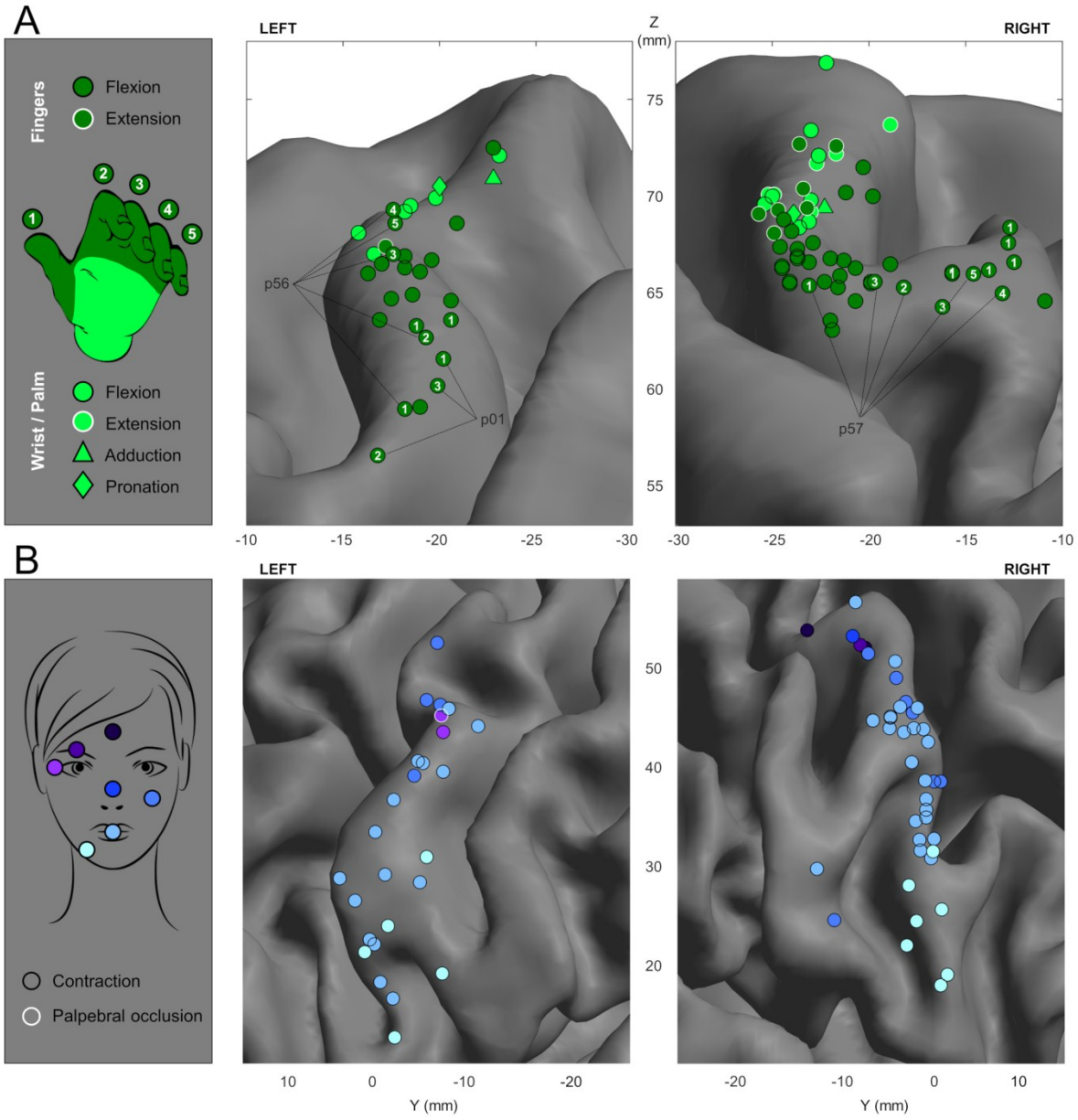

Figure 3. The motor somatotopic sequences of the hand and face

A: Detected movements of the wrist (light green) and of all or individual fingers (dark green). For the individual finger movements, numbers indicate the activated finger. Overall, individual finger movements were detected more laterally than global finger contractions. P1, p56, and p57 (patient 1, 56, and 57, as detailed in table 2) show the 3 individuals who had multiple recordings of individual fingers. **B:** Detected movements for the face. There is a medial-to-lateral somatotopic sequence for the forehead (dark purple), eyebrows (medium purple), eyes (light purple), nose (dark blue), cheeks (medium blue), both lips (pale blue), and chin (very pale blue). Face movements were contractions (black outline) with the exception of a palpebral occlusion (white outline).

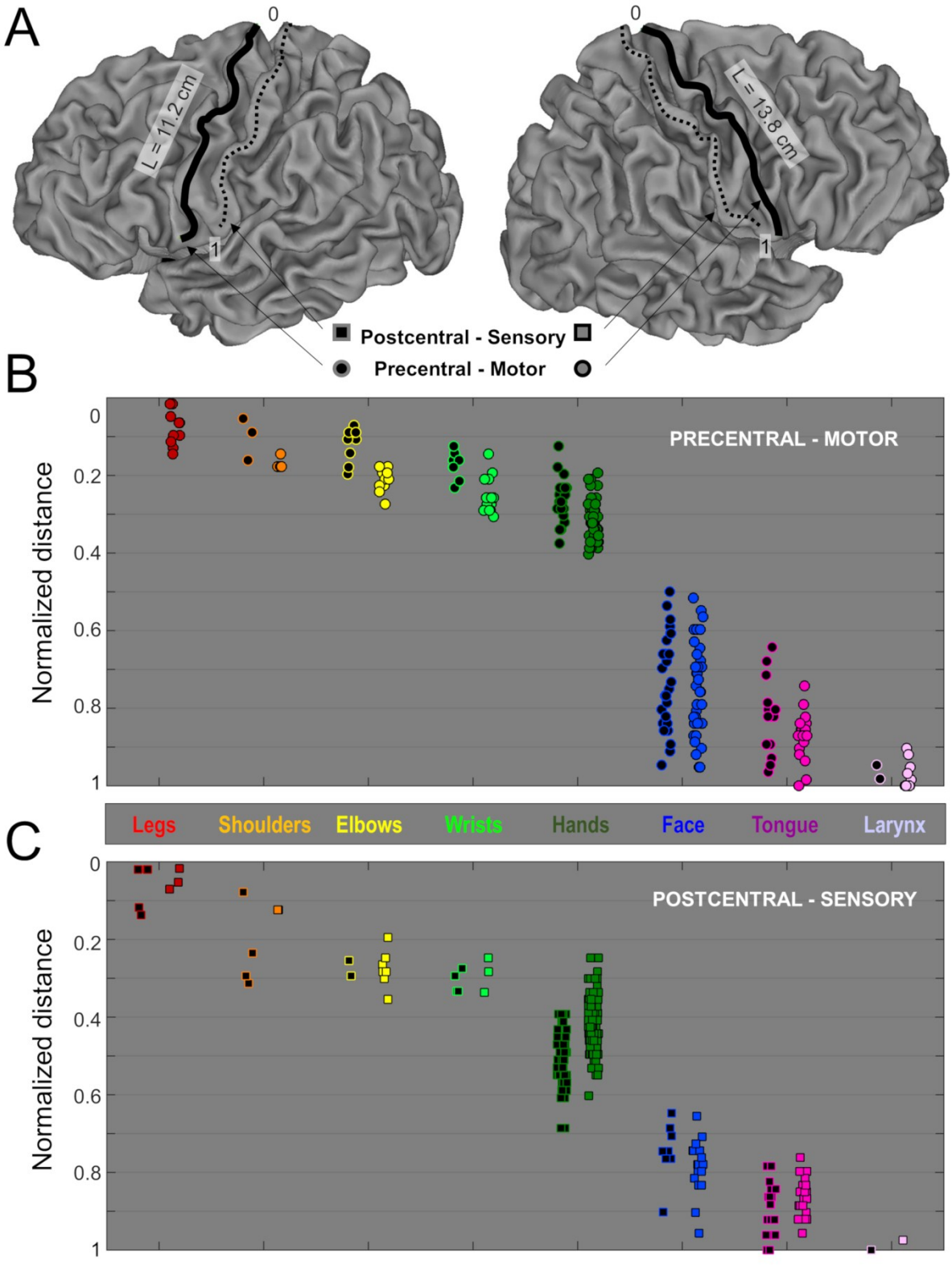

Figure 4. Anatomical relative variations of the human motor cortex compared with our previously published somatosensory data

A: Representation of the paths drawn along the crown of the precentral gyrus in the left and right hemispheres for the current study (thick black lines in the left and right images, respectively). The dotted lines along the postcentral gyrus are those that were used to map the sensory somatotopic sequence in our previous study (Roux *et al.*, 2018). The normalized distance of the positive stimulation sites was quantified along these paths, from 0 (medial extremity) to 1 (lateral extremity). **B:** Normalized distances for the different motor representations and for the left and right hemispheres (symbols with darkened centers indicate the left hemisphere). Except for leg representations, which were encountered by chance only in the right hemisphere, the representations exhibit very little interhemispheric variability in terms of mean distance and dispersion. The variabilities observed were probably due to the template we used, which was not strictly symmetric. **C:** Normalized distances for the somatosensory representations from our previous study (Roux *et al.*, 2018).

Table 1. Number and localization of cortical sites stimulated in patients

Left and right hemispheric regions stimulated	Number of stimulations (n = 2545)
Precentral gyri	608
Postcentral gyri	275
Supramarginal gyri	149
Upper parietal	51
Superior temporal gyri	232
Middle temporal gyri	95
Superior frontal gyri	483
Middle frontal gyri	458
Inferior frontal gyri	194

Table 2. Type of movement detected

	Contraction	Flexion	Extension	Abduction	Adduction	Pronation	Other	Total
Foot			4					4
Knee		1						1
Hip		4						4
Buttocks	1							1
Shoulder		1		2	1		3*	7
Elbow		17	3					20
Wrist		14	6		2	2		24
Fingers		41	8					49
Thumb		11						11
2nd finger		3						3
3rd finger		4						4
4th finger		2						2
5th finger		2						2
Eyebrow	1							1
Eyelid	1						1**	2
Forehead	2							2
Lip	38							38
Cheek	11							11
Nostril							1***	1
Jaw	12							12
Tongue	35							35
Larynx	14							14
Total	115	100	21	2	3	2	5	**248**

The 2nd finger refers to the index finger, the 3rd finger to the middle finger, the 4th finger to the ring finger, and the 5th finger to the little finger.

*Shrugging of the shoulder.

**Opening of the eyelid.

***Opening (dilatation) of the nostrils.

Table 3. MNI coordinates, barycentres (bold) and standard deviations (italic) of inferior limb, fingers, and face regions. In group analysis, Table 3B shows that the thumb area (mean of absolute values of X coordinates : 35.27) was located within other individual finger areas (mean of absolute values of X coordinates 35.54). We could not detect either a clear somatotopy for the thumb with respect to the other fingers or for the other fingers taken individually.

A. Inferior Limb				
Patient ID	X (mm)	Y (mm)	Z (mm)	Body Part
5	2	-33	74	Foot
26	3	-34	74	Foot
88	6	-33	74	Foot
91	10	-32	74	Foot
26	7	-31	75	Knee
23	10	-30	76	Hip
26	13	-28	77	Hip
27	11	-27	77	Hip
48	8	-16	74	Hip
91	12	-29	76	Buttock
Mean	**|8.2|**	**-29.3**	**75.1**	—
SD	*3.7*	*5.2*	*1.3*	—
B. Individual Fingers				
Patient ID	X (mm)	Y (mm)	Z (mm)	Body Part
1	-36	-21	64	Thumb
19	-37	-19	63	Thumb
25	-38	-20	62	Thumb
39	36	-16	66	Thumb
49	33	-13	67	Thumb
52	27	-13	68	Thumb
52	32	-13	68	Thumb
56	-42	-18	59	Thumb
57	36	-23	65	Thumb
58	36	-16	66	Thumb
58	35	-14	66	Thumb
1	-44	-17	57	2nd finger
56	-38	-19	63	2nd finger
57	36	-18	65	2nd finger
1	-40	-20	60	3rd finger
56	-32	-18	67	4th finger
57	37	-21	65	4th finger
80	37	-16	64	4th finger
56	-29	-18	69	4th finger
57	36	-15	66	4th finger
56	-26	-18	69	5th finger

57	36	-13	65	5th finger
Mean	**|35.4|**	**-17.2**	**64.7**	**—**
SD	*4.3*	*2.9*	*3.1*	—
C. Face				
Patient ID	X (mm)	Y (mm)	Z (mm)	Body Part
49	42	-12	55	Forehead
55	45	-6	53	Forehead
13	45	-6	53	Eyebrows
16	-51	-6	46	Eyes
19	-53	-6	44	Eyes
11	44	-7	54	Nose
1	-44	-5	53	Cheek
4	-55	-3	40	Cheek
8	-46	-4	48	Cheek
26	53	-1	46	Cheek
28	-48	-5	47	Cheek
37	60	-9	25	Cheek
38	52	2	39	Cheek
49	50	-2	50	Cheek
66	49	-1	47	Cheek
66	46	-5	52	Cheek
72	51	2	39	Cheek
14	-59	2	22	Jaw
24	61	2	18	Jaw
39	60	0	25	Jaw
66	61	-1	22	Jaw
66	61	-1	28	Jaw
66	60	1	32	Jaw
71	-57	-1	13	Jaw
72	61	3	19	Jaw
72	60	1	25	Jaw
96	-56	-4	31	Jaw
99	-61	-6	19	Jaw
99	-60	0	24	Jaw
Mean	**|53.5|**	**-2.7**	**36.9**	**—**
SD	*6.5*	*3.8*	*13.5*	—

SD = standard deviation.

Table 4. MNI coordinates, barycentres (bold) and standard deviations (italic) of shoulder, elbow, wrist, all fingers, lips, tongue, and larynx body regions.

A. Shoulder			
Patient ID	X (mm)	Y (mm)	Z (mm)
5	18	-24	75
8	-22	-26	75
14	-26	-20	70
18	11	-15	75
27	19	-23	75
61	15	-19	74
70	-18	-26	76
Mean	**|18.5|**	**-21.7**	**74.4**
SD	*4.6*	*3.8*	*2.2*
B. Elbow			
Patient ID	X (mm)	Y (mm)	Z (mm)
5	24	-23	73
14	-27	-17	69
15	-24	-24	74
17	20	-23	74
18	15	-17	75
21	-24	-21	72
27	23	-22	73
42	21	-21	74
48	15	-15	74
50	25	-25	71
51	-23	-23	74
56	-23	-24	74
57	29	-25	70
60	-26	-20	70
61	19	-21	73
70	-21	-26	76
78	25	-22	72
78	25	-25	71
90	-23	-24	74
95	-23	-25	75
Mean	**|22.6|**	**-22.1**	**72.8**
SD	*3.6*	*2.8*	*1.8*
C. Wrist			
Patient ID	X (mm)	Y (mm)	Z (mm)
8	-23	-20	71

8	-26	-23	71
14	-32	-17	67
15	-26	-19	70
17	22	-23	73
18	20	-23	72
20	17	-19	74
25	-30	-16	68
27	28	-23	70
33	31	-23	69
42	22	-23	72
50	29	-25	70
51	-25	-20	70
55	21	-22	72
56	-25	-23	72
57	32	-24	68
58	27	-25	70
58	33	-25	67
60	-27	-18	69
69	16	-22	77
78	29	-25	70
78	28	-22	69
87	28	-25	70
88	32	-25	68
Mean	**|26.2|**	**-22.1**	**70.4**
SD	*4.7*	*2.7*	*2.3*
D. All Fingers			
Patient ID	X (mm)	Y (mm)	Z (mm)
2	25	-20	72
5	35	-21	66
7	-35	-21	65
7	-32	-18	67
8	-33	-17	67
9	-35	-18	65
9	-33	-18	66
14	-35	-19	65
20	26	-21	70
21	-33	-21	69
23	32	-24	68
25	-33	-16	66
26	35	-24	66
28	-36	-17	64
30	27	-23	70
30	24	-22	73
31	34	-22	67
32	34	-24	67
36	36	-22	65
39	37	-21	65

40	-31	-17	67
41	35	-24	66
42	31	-25	69
50	33	-25	67
53	34	-24	67
55	27	-20	70
57	32	-25	68
57	34	-25	66
58	30	-26	69
58	35	-24	66
58	36	-22	66
58	36	-20	66
58	34	-11	65
59	36	-20	66
60	-33	-19	66
61	33	-23	68
61	34	-24	67
61	36	-22	66
65	-35	-20	67
70	-24	-23	73
78	31	-24	69
80	37	-22	63
81	37	-22	64
83	36	-20	66
86	34	-25	66
88	30	-23	69
88	34	-21	67
89	23	-24	73
93	-41	-19	59
Mean	**|32.9|**	**-21.4**	**67.0**
SD	*3.8*	*3.0*	*2.6*
E. Lips			
Patient ID	X (mm)	Y (mm)	Z (mm)
2	58	1	37
3	-56	-1	37
6	-54	-4	41
6	-56	1	34
12	60	0	32
13	58	1	32
14	-50	-6	47
16	-58	3	27
19	-57	5	29
29	54	-1	45
39	55	-3	45
43	-57	0	30
44	-56	-1	17
46	-54	-6	40

47	-59	2	23
47	-57	1	18
53	49	0	47
54	55	-2	44
58	42	-7	58
62	54	0	35
62	54	1	43
62	48	-3	52
66	58	1	35
66	56	1	39
67	59	1	31
67	53	1	36
69	57	0	33
69	62	-11	30
71	-54	-3	41
72	55	-1	41
72	54	-3	46
73	-59	1	22
74	-51	-9	45
76	54	-3	46
76	51	0	44
77	54	-3	46
82	54	-5	45
97	-58	-3	29
Mean	**|55.0|**	**-1.4**	**37.4**
SD	*3.7*	*3.3*	*9.3*
F. Tongue			
Patient ID	X (mm)	Y (mm)	Z (mm)
10	58	1	32
16	-57	1	18
24	60	1	25
29	60	1	27
29	54	0	35
34	59	0	30
35	-57	3	27
44	-57	0	8
47	-57	-2	14
63	61	-1	30
63	61	-1	30
64	61	-2	29
64	59	0	34
64	56	-1	39
66	61	1	11
66	62	1	17
67	60	3	22
68	60	2	26
71	-59	-3	27

71	-57	2	29
71	-56	-2	37
72	60	1	29
72	56	0	34
73	-57	-2	11
73	-56	-1	17
74	-54	-5	41
75	-60	-1	24
77	60	1	20
77	60	1	26
77	57	-1	32
80	60	1	27
92	-59	2	23
92	-58	3	27
96	-51	0	40
100	-60	-4	26
Mean	**|58.3|**	**0.0**	**26.4**
SD	*2.4*	*1.9*	*8.2*
G. LARYNX			
Patient ID	X (mm)	Y (mm)	Z (mm)
22	60	2	13
34	61	3	12
34	61	3	19
45	62	2	12
63	61	-3	24
64	61	-3	21
67	60	3	15
77	61	3	12
79	60	3	15
80	60	2	13
84	60	4	13
85	60	3	11
94	-58	-8	9
98	-58	1	7
Mean	**|60.2|**	**1.1**	**14.0**
SD	*1.1*	*3.4*	*4.6*

Table 5. Results of the 3-way ANOVA (full model) with the normalized distances as dependent variables (see Figs. 4B and 4C) and with the somatotopy (body part representations, F1), the laterality (left/right hemisphere, F2), and the domain (motor/sensory, F3) as the 3 independent factors (df: degree of freedom; SSQ: sum of squares). The full model accounts for 73.7% of the observed variance, revealing a moderate between-subjects variability. By itself, the somatotopy accounts for 71% of the variance (versus 0.01% and 0.53% for the laterality and domain, respectively). These results imply that despite statistically significant modulations, the somatotopy is well preserved across the hemispheres and across the motor and sensory domains.

Source	df	SSQ	F value	P value	η^2 (%)
F1 : somatotopy	6	23.21	735.02	$<10^{-200}$	71.34
F2 : laterality	1	0.00	0.81	0.37	0.01
F3 : domain	1	0.17	32.81	$<10^{-7}$	0.53
F1 x F2	6	0.04	1.12	0.35	0.11
F1 x F3	6	0.41	12.97	$<10^{-12}$	1.26
F2 x F3	1	0.06	11.88	$<10^{-3}$	0.19
F1 x F2 x F3	6	0.08	2.57	0.02	0.25
Error	463	2.44			
Total	490	32.54			73.69