Review

Identification of multiple nonprimary motor cortical areas with simple movements

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Abstract

The human cortex reportedly contains at least five nonprimary motor areas: in the frontolateral convexity, the dorsal and ventral premotor cortex (PMd and PMv), and in the frontomesial wall, the presupplementary and supplementary motor areas (pre-SMA and SMA), and the rostral, dorsal and ventral cingulate areas (CMAr, CMAd, and CMAv). Activation of these regions in neuroimaging studies has been generally associated either with the performance of complex motor tasks or with reorganization occurring with motor recovery in the presence of pathology. Recent evidence from neuroimaging studies suggests that the same areas are activated with well controlled simple movements in healthy subjects providing support to the observation that their contribution may be more quantitative rather than exclusively specific to a certain aspect of motor behaviour. An important consequence of this observation is that activation of multiple nonprimary motor areas during simple motor tasks should not be considered unique to patients with upper or lower motoneuron lesions but rather as a normal physiological process. © 2001 Elsevier Science B.V. All rights reserved.

Theme: Motor systems and sensorimotor integration

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Contents

1. Introduction

1.1. Multiple motor areas in nonhuman primates

Physiological and anatomical investigations have con-

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vincingly demonstrated the existence of multiple motor areas in the frontal lobe of nonhuman primates [38,50,53]. The number varies from four to about 10 located on the lateral convexity and within the medial wall of the hemisphere. On the lateral convexity, in addition to the primary motor cortex (M1) which itself has occasionally been divided into two to three rostrocaudal fields [36], the premotor (PM) cortex contains two gross subdivisions: dorsal (PMd) and ventral (PMv). On the basis of histological and functional findings two subregions, rostral and caudal, respectively, have also been shown both in PMd and PMv [3,15,17,20,22,29,30,38]. Within the mesial wall, in addition to the supplementary motor area (SMA) first described by Woolsey et al. in 1952 [52], four new regions have been discovered, one in front of the SMA (pre-SMA) and three in the cingulate sulcus, the cingulate motor areas rostral, ventral and dorsal (CMAr, CMAv and CMAd, respectively) [21]. In most regions and for various motor tasks movement-related neuronal activity has been found. Whereas some motor areas appear to be involved in motor control in the same manner others, such as the pre-SMA and CMAr, seem to be highly specialized. For example, in the performance of a sequential motor task based on memory, a neuron population in the pre-SMA was only activated each time the monkey had to develop a new motor plan [42]. However, in a similar task some CMA neurons seemed specifically involved in reward-based selection, particularly in the CMAr [43]. On the basis of low-threshold microstimulation and anatomical connectivity a gross or partial somatotopical representation has been found in some of these regions [11,16]. However, a clear body representation has up to now only been convincingly demonstrated for the SMA [28].

1.2. Multiple motor areas in humans

The search for homologies of these multiple motor areas in the human brain and for their respective involvement in motor control has been attempted by many investigators using imaging techniques over the last decade. A constant finding with positron emission tomography (PET) and fMRI has been the activation of many areas during motor performance. However, the foci of activation within the frontal lobe were not always in the same location under the various experimental conditions. This suggests either a large degree of interindividual variability or of regional specialization. In their review, Picard and Strick [34] proposed some anatomical landmarks for the human motor areas within the mesial wall. They suggested on the basis of several PET investigations to reduce the CMAs into two zones, a caudal and a rostral one. The lateral convexity has not yet been analyzed in the same manner, and the boundaries for a parcellation of this region in several subregions are not yet drawn systematically. An attempt with immunohistochemistry has identified two fields in the dorsal PM cortex [1]. This SMI-32 immunoreactive tech-

nique provided 'neurofilament architecture' patterns specific to the two subdivisions of area 6, namely a caudal (area 6c) and a rostral one (area 6r). Another study on the basis of neurotransmitter receptor labelling has proposed two large PM subdivisions, 6aα and 6aβ [54].

In neuroimaging studies, motor tasks of various degrees of complexity activated a region rostral to the M1 hand region around the precentral and superior frontal sulcus, generally identified as PMd. Evidence for a ventral PM region is more sparse but has been lately suggested by the demonstration of activation close to the frontal operculum during complex tasks such as motor imagery [8,44], preparation for copied movement [26], and grasping movements or grasping observation [19,37].

Many important questions related to the multiple non-primary motor areas in the human cortex still remain unanswered: first, the degree of their somatotopical organization; second, the variability of the activation patterns between subjects, taking into account the individual anatomical specializations; third, the degree of their functional specialization and their homologies with those proposed in the monkey. In the present review, we address these issues pertaining to current neuroimaging research. Particularly, we critically address the regional functional specialization as reported by several studies under complex experimental conditions, and ask whether the same areas can also be activated by simple hand or foot movements. The ability to move our hand and foot is crucial to most human daily activities. Furthermore, simple hand and/or foot movements are extensively used in the clinical setting (i.e. preoperative planning), particularly since the widespread use of fMRI methodology in brain mapping. The presence of multiple cortical motor areas in the human brain, the uncertainty related to their precise localization, and the experimental conditions under which they may be activated often complicate the interpretation of changes in BOLD signal in the presence of pathology. Several areas in the ipsi- or contralateral hemisphere have been implicated in the process of functional reorganization after lesions in M1 or of the corticospinal tract [31,45,49]. Our report has thus for goal to discuss normal activation patterns when subjects execute simple and well controlled hand or foot movements, and focuses primarily on nonprimary motor areas, their topographical location in the human brain, and their gross somatotopical organization. We review the neuroimaging literature and, in addition, illustrate the relevant findings by two representative cases from our own experience using fMRI methodology.

2. Methodological issues

PET and fMRI are currently the most powerful neuroimaging techniques for mapping brain function. PET has been the gold standard until the mid-1990s, while fMRI has been increasingly used in this domain over the past

few years. There are multiple methodological issues that need to be considered when interpreting neuroimaging data, particularly when looking at nonprimary cortical areas. Although a detailed analysis is beyond the limited space of this review, some issues need to be briefly mentioned. These include the spatial resolution of the technique used, the replicability of data from brain to brain, the sensitivity, the type of postprocessing used to generate functional maps, the definition of regions of interest (ROIs), the display of the data, and issues related to the standardization of the experimental conditions [23]. An important advance is the ability to coregister the functional data with each individual's anatomical brain images to preserve individual gyral anatomy and to avoid intersubject averaging and anatomical blurring. fMRI is ideally suited for single-case studies, in which a large number of scans can be acquired repetitively in the same subject.

In this review we selectively report for illustrative purposes two right-handed [4] subjects (24-year-old female and 25-year-old male), from a group of 12 healthy volunteers. The data from each individual are analyzed separately to avoid intersubject averaging and to preserve individual gyral anatomy. Whole brain functional imaging is carried out on an 1.5-T whole body scanner using a gradient-echo, echo-planar pulse sequence sensitive to the blood oxygen level-dependent (BOLD) signal with an in-plane resolution of 2×2 mm and a slice thickness of 4 mm.

Examples of changes in BOLD signal are shown for two simple movements, self-paced at a rate of approximately 0.5 Hz: first, flexion/extension of all fingers together with the wrist fixed in a slight extension (15°, natural resting position of the hand); second, plantar (45°) and dorsal flexion (10°) of the right foot. Each activation experiment consists of 30 s rest alternating with 30 s movement periods. Standardization of movements is achieved by a custom designed forearm splint fixed on to the scanner table and by the use of appropriate strips and cast elements.

Data are analyzed on an individual basis using routine motion correction [51] and post-processing [2] algorithms. Voxels activated during the task conditions are identified by calculating non-parametric Spearman rank order correlation coefficients between the time series of pixel intensities and an idealized response function with a time shift of 4 s to account for the hemodynamic delay. Transformations to Student's *t*-statistics are made [35]; only pixels with statistically significant correlation ($P<0.001$, not corrected for multiple comparisons) are considered as activated. Using a fully automated procedure, anatomical reference volumes are co-registered to the Montreal average volumetric data set aligned on the Talairach stereotactic coordinate system [6]. To describe the results of the two subjects we use a region-of-interest (ROI) approach to define broader areas according to neuroanatomical and

neurophysiological studies in humans and nonhuman primates and, subsequently, we search for individual activation clusters within these areas. For each cluster the activation maxima and the maximum signal intensity (maximum *t*-value) are determined and their location in Talairach coordinates retained. Additionally, for topographical clarity, particularly on the mesial surface and insular region, all statistically significant data are displayed on inflated cortical surface, as described [7,41] using the FreeSurfer software (www.nmr.mgh.harvard.edu/freesurfer).

3. Activation of multiple motor areas with simple movements

Reports investigating systematically the topography and extent of activation of nonprimary motor cortical areas in humans associated with simple motor tasks of hand or foot are scarce in the recent neuroimaging literature. Probably the most interesting and relevant one is that by Fink et al. using PET [13]. These authors demonstrated activation of multiple nonprimary motor areas in the contralateral hemisphere of three individual subjects with simple movements of hand, shoulder or leg. They showed a general topographical arrangement of activity in the lateral and mesial wall of the frontal cortex almost similar to that observed in our volunteers using fMRI. In the following, we systematically present the areas of activation separately in the lateral and the mesial wall as illustrated by our two representative cases (Figs. 1 and 2) and by the review of the literature pertaining to the anatomical localization of these regions, their functional specialization, and potential somatotopical organization. Additionally, the distribution of activity in the ipsilateral hemisphere is separately discussed with emphasis on the occurrence of ipsilateral M1 activation. Table 1 gives in detail the respective coordinates of the activation maxima for the contra- and the ipsilateral hemisphere associated with movements of right hand and foot for each subject. This table demonstrates that both body parts are represented in most motor areas of the contra- and ipsilateral hemispheres in both subjects.

3.1. Activation in the lateral wall

On the lateral surface of the contralateral hemisphere (Fig. 1, LH) the hand lies within the central sulcus (M1). Anterior to the central sulcus, along the precentral gyrus and partially within the precentral sulcus we clearly identify two individual clusters: a dorsal one, above the junction of the middle frontal with the precentral gyrus and a ventral one below (Fig. 1A). These two separate clusters of activity along the PM cortex most probably correspond to the PMd and PMv areas of the monkey. The activation maxima for the dorsal region are located between 53 and
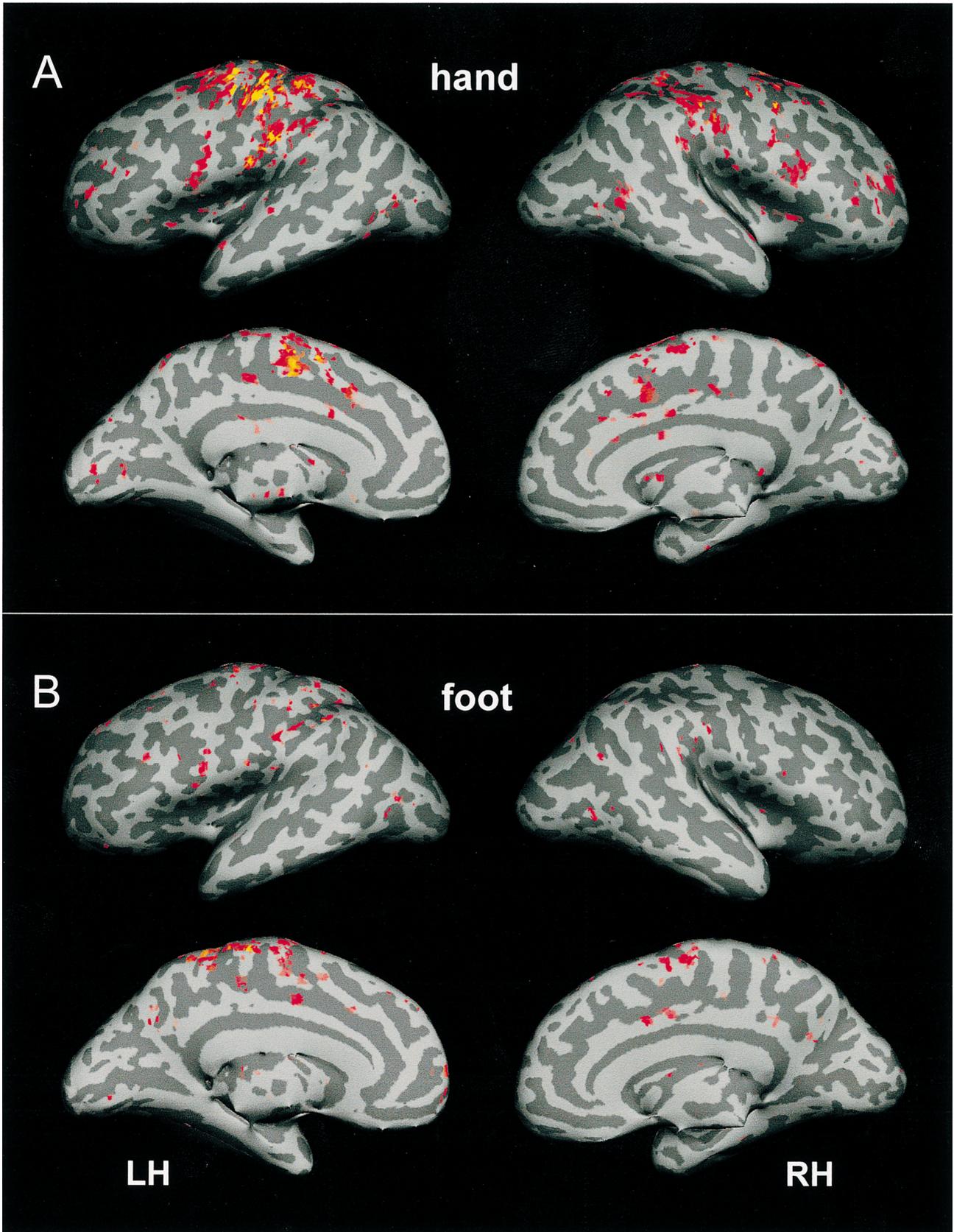
66 mm above the AC–PC line and 3 mm anterior to 13 mm posterior to the VAC line, (Table 1). Despite the uncertainties in the human brain regarding the separation of the human dorsal PM cortical area from M1 caudally and from the prefrontal cortex rostrally [14,54], consistent activation has been demonstrated in many functional studies using various motor tasks such as movements guided by sensory information, movements triggered or paced or cued by sensory signals, as well as non-over-learned self-generated movements [40]. According to Zilles et al. [54], the VAC line further subdivides this region into an anterior area (6aα) and a posterior one (6aβ). The lack of anatomical landmarks on the cortical surface to further separate the fMRI clusters observed in this region, leads us to identify them grossly as a single functional field extending within and around the precentral sulcus, and above the junction of the middle frontal with the precentral gyrus. The local maxima for hand movements are consistently located anterior to that for the foot suggesting a somatotopical gradient in this dorsal PM area (Table 1).

The ventral area of activation within the PM cortex extends from the junction of the middle frontal with the precentral gyrus dorsally to the fronto-opercular region ventrally (Fig. 1A). Its coordinates range between 12 and 26 mm above the AC–PC line and 5–13 mm anterior to the VAC line, with an overlap of both extremities (Table 1). Similar to dorsal PM area, the fMRI data suggest a further subdivision of this region into multiple clusters encompassing opercular area 6, but also part of area 44, and the rostral upper bank of the Sylvian fissure. To what extent this region can be subdivided into further subregions is still unclear. In the ventrolateral precentral cortex and/or anterior insula, activation has been reported in relation to movements guided by sensory feedback, motor imagery, observation of actions, or motor preparation of copied finger movements [10,19,26,37,40,44]. Increased PET activity with simple movements has also been reported in this region in patients recovering from striatocapsular infarction [5,45,49]. To our knowledge, only the PET study by Fink et al. [13] and our own observations describe activation of these regions associated with simple movements in healthy subjects. Fink et al. [13] demonstrated opercular and insular activation with simple finger, shoulder and leg movements without extension into area 44. However, a more recent study requiring simultaneous or separate movements of the upper and lower limbs reports activation in the contralateral ventral PM cortex including area 44 [12]. To what extent the PM subdivisions contain a full representation of the somatomotor apparatus is not clear [40]. In our subjects, bilateral activation of the ventral PM cortex occurs with both hand and foot simple movements. This foot representation in human ventral PM area is quite surprising as microstimulation studies in macaque monkey have only reported finger and hand or facial movements in this region [16,22,39]. In general, despite the smaller degree of activity elicited by foot compared to hand movements a similar topographical location of activated clusters is seen for both body parts extending into area 44 (Fig. 1B).

Although not treated as nonprimary motor areas, multiple areas are also activated in the parietal cortex, including the primary somatosensory area (S1, within the posterior bank of the central sulcus), the secondary somatosensory corte (S2, in the upper bank of the Sylvian sulcus), superior and inferior parietal areas (superior and inferior to the intraparietal sulcus, respectively) of both subjects, similar to the report of Fink et al. [13].

3.2. Activation in the mesial wall

The distribution of activity in the mesial surface of the flattened cortex (Fig. 1) and in the parasagittal sections (Fig. 2) reveals several clusters associated both with hand and foot movements. In the contralateral hemisphere (Fig. 1B, LH), foot movements elicit significant activation in the anterior bank of the marginal ramus of the central sulcus corresponding to M1. The multiple activation clusters in nonprimary motor areas can be separated into a dorsal group along the superior frontal gyrus (SMA), and a ventral group located within or just adjacent to the cingulate sulcus (CMA). In the anterior–posterior direction, these clusters extend from the marginal ramus of the central sulcus towards the splenium of the corpus callosum, however without reaching it. By simple visual inspection, the activation clusters in the mesial wall can be grouped into a rostral and a caudal area. The rostral area comprises the pre-SMA in the superior frontal gyrus and the CMAr within the cingulate sulcus. The caudal group contains the SMA proper in the superior frontal gyrus and two separate cingulate clusters, a large dorsal one just above the sulcus (CMAd) and a small ventral one within the sulcus (CMAv).

In the monkey, the mesial wall is known to contain four premotor areas that project directly to both the primary motor cortex and the spinal cord (SMA, CMAr, CMAd, and CMAv) [21,46]. In addition, a fifth motor field, the pre-SMA, lies rostral to SMA and is interconnected with

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Fig. 1. Cluster maps of significant cerebral activation in subject 1 during movements of right hand (A) and foot (B). The clusters are superimposed on the lateral (top row) and medial (bottom row) flattened cortical surfaces of the hemisphere contralateral (LH) and ipsilateral (RH) to the moving limb. These displays demonstrate the relationship of fMRI activation foci to the individual gyri and sulci on the brain surface reconstructed from high-resolution MR images. The lateral surfaces show activation areas for hand movements in the primary motor (M1) and somatosensory (S1) cortex, dorsal and ventral premotor (PM) cortex, superior and inferior parietal areas, and secondary somatosensory cortex (S2). The mesial surfaces show significant activation for foot movements in M1 and S1, supplementary motor cortex (SMA), pre-SMA, and rostral, dorsal and ventral cingulate motor areas.
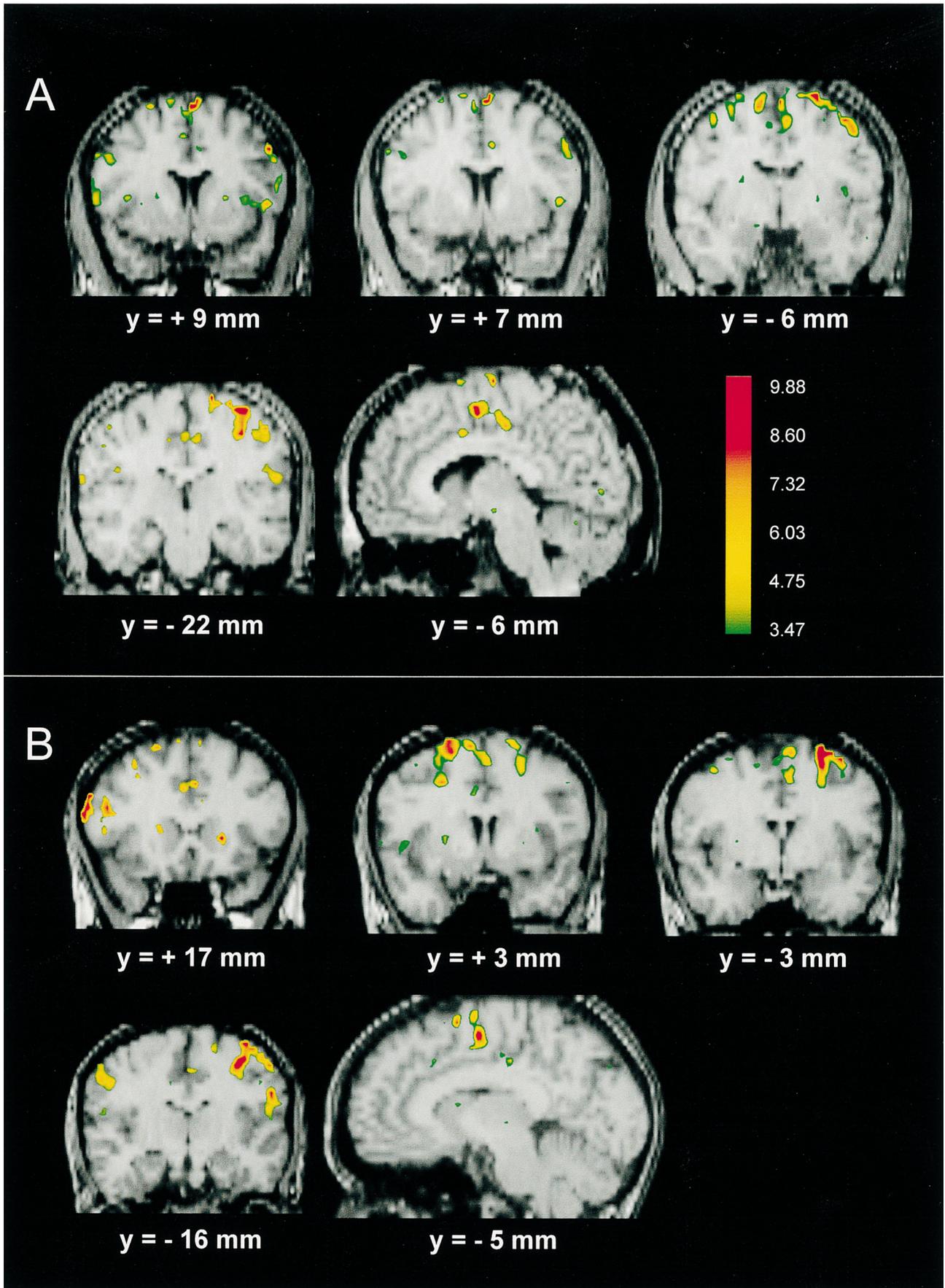
Table 1
Talairach coordinates of local maxima of cortical clusters showing significant ($P<0.001$) activity associated with simple movements of the right hand and foot in two single subjects

Functional area	Brodmann area	Body part	Subject 1						Subject 2					
			Contralateral hemisphere			Ipsilateral hemisphere			Contralateral hemisphere			Ipsilateral hemisphere		
			x	y	z	x	y	z	x	y	z	x	y	z
M1	BA 4	Hand	−38	−16	59	41	−7	56	−36	−15	56	43	−3	56
		Foot	−2	−29	64	–	–	–	−2	−24	68	–	–	–
SMA	BA 6	Hand	−3	−7	69	12	−5	68	−6	−2	68	6	−3	72
		Foot	−4	−10	67	9	−8	69	−8	−8	67	11	−6	66
preSMA	BA 6	Hand	−2	9	67	5	7	64	–	–	–	10	5	69
		Foot	−2	8	67	5	7	66	–	–	–	–	–	–
PMd	BA 6	Hand	−25	−10	63	32	−5	63	−41	1	54	35	3	58
		Foot	−15	−13	66	29	−7	59	−31	−6	53	39	0	55
PMv	BA 6, 44	Hand	−54	5	20	56	11	18	−50	12	12	56	13	12
		Foot	−54	8	17	56	12	12	−53	6	26	51	9	15
CMAd	BA 6	Hand	−5	−9	52	4	−11	−51	−4	−5	56	2	−14	51
		Foot	−5	−2	50	6	−7	56	−3	−9	55	6	−8	60
CMAv	BA 31	Hand	−6	−20	44	12	−23	44	−6	−20	44	12	−17	39
		Foot	−12	−25	44	14	−22	39	−10	−23	43	12	−22	40
CMAr	BA 24/32	Hand	−6	9	40	6	7	44	−5	7	42	7	15	42
		Foot	−6	16	40	6	8	45	−6	7	41	7	9	42
S1	BA 3, 1, 2	Hand	−34	−32	54	–	–	–	−37	−33	58	–	–	–
		Foot	−8	−47	68	–	–	–	−6	−34	69	–	–	–
Superior parietal	BA 5	Hand	−50	−28	56	48	−31	56	−35	−36	60	36	−36	59
		Foot	−12	−44	60	13	−49	70	−8	−40	67	–	–	–
Inferior parietal	BA 40	Hand	−57	−13	40	55	−11	47	−52	−24	42	62	−26	24
		Foot	−52	−18	40	56	−18	36	−48	−32	46	60	−17	36
S2	BA 40/43	Hand	−58	−22	20	62	−14	24	−56	−16	31	64	−10	12
		Foot	−58	−25	20	63	−18	19	−52	−25	23	–	–	–

Coordinates in mm: x, distance to right (+) or left (−) of midsagittal line; y, distance anterior (+) or posterior (−) to vertical plane through anterior commissure (VAC); z, distance above (+), or below (−) intercommissural (AC–PC) line. BA, estimate of Brodmann area according to Talairach and Tournoux [6]. M1, primary motor cortex; SMA, supplementary motor area; PMd, premotor dorsal; PMv, premotor ventral; CMAd, cingulate motor area dorsal; CMAv, cingulate motor area ventral; CMAr, cingulate motor area rostral; S1, primary somatosensory cortex; S2, secondary somatosensory cortex. For the regions with more than one activation maximum, this table gives the geometrical center of all local maxima.

prefrontal and nonprimary motor areas [34]. In human, functional imaging studies demonstrated activation in the mesial wall related to various aspects of motor behaviour such as movement execution, response selection, motor learning, motor planning, bimanual coordination, and even motor imagery (see Ref. [34] for review). However, the absolute identification of separate motor fields and their specific contributions to motor behaviour are not yet fully clarified. The classification of Picard and Strick [34], based on more than 30 functional imaging studies (mainly PET), into two dorsal areas (SMA and pre-SMA) and two ventral cingulate zones provides a practical framework. These authors conclude that tasks requiring higher order aspects of motor control produce activation rostral to VAC line in pre-SMA, whereas simpler motor tasks lead to activation caudal to the VAC line in SMA proper. However, they do mention that electrical stimulation, evoking movements both rostral and caudal to the VAC line in humans, has not resulted in a clear distinction between these two areas. In our representative cases, activation both anterior (pre-SMA) and posterior (SMA) to the VAC line is elicited by simple movements. The activation maxima of these two dorsal clusters lie 64–69 mm superior to the AC–PC line (Table 1). Activation in SMA is consistent and bilateral in both subjects and for both body parts. Its maxima lay within 2–10 mm posterior to the VAC line and have a clear

Fig. 2. Coronal and sagittal sections for subjects 1 (A) and 2 (B) during opening and closing of the right hand after coregistration of significant ($P=0.001$) functional MRI maps on the individual high resolution MR images. The two coronal cuts rostral to the vertical plane through the anterior commissure (VAC) demonstrate activation clusters in the ventral and dorsal premotor (PM) cortex, in the pre-supplementary motor area (pre-SMA), rostral cingulate area, and in the putamen. The coronal cuts caudal to the VAC show activity in the primary sensorimotor cortex (M1/S1) of the contralateral (left) hemisphere, in SMA, rostral and ventral cingulate areas, inferior parietal cortex and secondary somatosensory cortex (S2). The parasagittal cut through the left hemisphere (6 mm from the midline) reveals activation in SMA and pre-SMA dorsally and in rostral, dorsal and ventral locations within and adjacent to the cingulate sulcus. To localize the exact position of the maxima in these clusters (given in Table 1) the brain of each subject is transformed into Talairach and Tournoux stereotaxic coordinate system [6], retaining the individual gyral anatomy.

somatotopical organization with the hand located in front of the foot (Table 1). Activation in pre-SMA is less consistent and seen in one subject bilaterally for both hand and foot, but in the other ipsilaterally for hand movements only. Its maxima are located 5–9 mm anterior to the VAC line. This last finding differs from Fink et al. [13] who failed to activate the pre-SMA with simple movements. This difference may be related to the methodological sensitivity and lower spatial resolution of PET compared to fMRI. Another factor that may influence activity in pre-SMA is whether movements are externally cued as in Fink et al. or self-paced as in our experimental setting. In fact, a recent fMRI study revealed more extensive increase in BOLD signal in pre-SMA during self-initiated than during externally triggered movements [9]. The same study found a significant preponderance of ipsilateral response in pre-SMA suggesting a complex interhemispheric distribution of activity in this region that may explain the lack of contralateral activation in one of our subjects.

In the ventral mesial wall, activity is distributed along the cingulate sulcus and shows three main subdivisions, with one area located rostral (7–16 mm anterior to the VAC line), and two areas caudal to the VAC line (Table 1). In their review, Picard and Strick [34] conclude that the rostral zone is more specialized for complex motor tasks and the caudal zone for simpler ones (a functional division similar to pre-SMA and SMA). They also report within the rostral zone two separable areas, one anterior closer to the genu of the corpus callosum and another posterior closer to the VAC line. In our observations, similar to that of Fink et al. [13], activity is detected only in the more posterior part of the rostral zone, ranging between 7 and 15 mm in front of the VAC line. In contrast, in the caudal zone the clarity of two separate areas (Fig. 2) leads us to use the terminology employed for the monkey brain [54] as seen in Table 1. One area is located more dorsally and anterior, in the dorsal bank of the cingulate sulcus (50–56 mm above the AC–PC line and 2–11 mm behind the VAC line), probably corresponding to the CMAd of the monkey brain. The other one, probably the homologue of the monkey CMAv, is more ventral and posterior, in the ventral bank of the cingulate sulcus (30–44 mm above the AC–PC line and 17–25 mm behind the VAC line). The CMAs are buried in the cingulate sulcus, and the large variability of its course in the human brain [33,48] makes accurate localization difficult when data from several subjects are averaged in a common coordinate system. We want to emphasize that the only reliable approach for accurate identification of motor areas in the mesial wall is the single subject analysis with high-resolution anatomical and functional data that can be obtained with MR technology (Fig. 2). Inflating the cortical brain surface helps significantly to localize the caudal areas in the dorsal or ventral bank of the sulcus (Fig. 1). Activation is bilateral and qualitatively more pronounced in the hemisphere contralateral to the movements with larger activation foci

in CMAd (Fig. 1). This last observation is in accordance with Deiber et al. [9] who showed that the caudal zone was the only area with a significant response to every motor variable (type of motor task, movement, and rate) tested in their study. Our observations and the review of the literature do not provide any evidence for a consistent topographical organization of hand and foot representations in any of the CMAs.

3.3. Ipsilateral activation

There are no systematic investigations and descriptions of the distribution of activation in the ipsilateral nonprimary motor cortical areas associated with simple movements of either the hand or the foot. In our experience multiple clusters of significant activity are present ipsilaterally in mirror positions on the lateral and mesial surfaces, albeit with a smaller spatial extent compared to the contralateral hemisphere (Fig. 1, RH). The M1 activation on the lateral surface is reduced to a small focus in the anterior bank of the central sulcus, without involvement of S1 in the postcentral gyrus. However, there is a clear activity within and around the dorsal and ventral segments of the precentral sulcus and in the superior and inferior parietal areas. On the mesial surface, two clusters are seen in the dorsal part of the superior frontal gyrus corresponding to pre-SMA and SMA, and several small foci within and around the cingulate sulcus.

With respect to M1, ipsilateral activation is still a matter of debate, particularly for hand movements. The traditional view is that proximal arm movements are under bilateral control, whereas hand and fingers movements are exclusively controlled by the contralateral hemisphere. However, in a simple, highly controlled motor task involving distal muscles in monkeys, Tanji and collaborators [47] found activity related to ipsilateral finger movements in about 8% of the precentral cortical neuronal population. Functional imaging studies in humans have suggested that ipsilateral M1 activation mainly depends on task features and only occurs with more complex paradigms [18,24,27]. In a recent fMRI study, activation in the ipsilateral posterior precentral gyrus related to finger movements was interpreted as belonging to PM cortex extending over the gyral surface into the central sulcus [32]. The border between areas 4 and 6 is still ill defined [54], and it is possible that ipsilateral activation actually is partially located in area 6. It is also highly probable that detection of ipsilateral activation is dependent on the sensitivity of the method. A fMRI study at high magnetic field strength [25] revealed consistent activation in the ipsilateral M1 during a simple motor task of sequential finger tapping, however 20 times smaller and of 2.3 times less intensity than contralaterally. In the two illustrated cases, the ipsilateral M1 hand representation is clearly separated from that detected in PM within and adjacent to the precentral sulcus in both subjects. Overlay of the activation maps on

the flattened cortical surface helps making this distinction clear as seen on the lateral surface of the hemisphere ipsilateral to the moving hand in Fig. 1 (RH).

Activation related to foot movements is detected only in the contralateral M1. Its absence in the ipsilateral hemisphere may reflect the smaller cortical representation of this body part related to its poor functionality compared to the hand, or may be caused by the smaller amplitude of the ankle movements required to avoid associated fMRI artefacts. In fact, we always observe much less activation for foot than for hand movements in all primary and nonprimary motor areas (Fig. 1). However, despite the much smaller degree of activity compared to hand movements a topographical arrangement of the nonprimary activation clusters is seen ipsilaterally, similar to that of the contralateral hemisphere.

4. Conclusions

The present illustrative cases and the review of the relevant literature demonstrate that many cortical regions in the human brain are consistently and bilaterally activated by simple limb movements. These observations provide further support to the statement by Roland and Zilles [40] that 'complex sequences activate the same areas like simple movements indicating that activation associated with simple and complex movements may be more a matter of degree of activation than truly differential activation'. In addition to the information provided by the literature, the illustrative cases show that significant activation can be detected in single subjects during simple movements in multiple cortical areas of the lateral and mesial cortex bilaterally, with slight differences in distribution depending on subject, hemisphere and body part.

The view that the mesial and lateral walls contain multiple motor areas and that these areas are also activated to a certain degree during simple movements is a relatively new concept for human studies. There is still little converging and convincing physiological information about all these cortical fields in humans. Some of these areas such as the SMA and dorsal PM show a tendency for somatotopical organization, whereas others such as the CMAs and ventral PM do not. With respect to the ventral PM, its location, spatial extent and functional specialization are not yet clear in humans. In our experience the ventral PM is located quite low and extends to the frontal operculum. Although most reports to date emphasize its activation with higher cognitive functions, this region not only activates bilaterally with simple limb movements, but also shows a colocalization of hand and foot representations. Existing parcellations of the nonprimary motor areas are still provisional, and further development of these tentative maps is expected as additional data become available.

An important consequence of these observations is that activation of multiple nonprimary motor areas during a simple motor task should not be considered unique to patients with upper or lower motoneuron lesions but rather as a normal physiological process. Knowledge of the activation patterns in healthy subjects should allow us to interpret those of patients more rationally. In particular, quantitative variables such as extent of activation and percentage of signal intensity rather than activation patterns alone should be investigated in the presence of pathology. These may more likely reflect changes in activity and in recruitment of additional sensorimotor areas due to an increasing attention demand or to cortical reorganization with restitution of motor function.

In the present study, we employed motor tasks of great simplicity that required no cognitive response, in an effort to activate the motor system solely and not to increase the discomfort of the subjects or lengthen the examination time. In view of the limited cooperation of the patients these issues are of importance when designing fMRI tasks for clinical application.

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