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Functional neuroanatomy of the primate isocortical motor system

Accepted: 3 July 2000

Abstract The concept of the primate motor cortex based on the cytoarchitectonic subdivision into areas 4 and 6 according to Brodmann or the functional subdivision into primary motor, supplementary motor, and lateral premotor cortex has changed in recent years. Instead, this cortical region is now regarded as a complex mosaic of different areas. This review article gives an overview of the structure and function of the isocortical part of the motor cortex in the macaque and human brain. In the macaque monkey, the primary motor cortex (Brodmann's area 4 or area F1) with its giant pyramidal or Betz cells lies immediately anterior to the central sulcus. The non-primary motor cortex (Brodmann's area 6) lies further rostrally and can be subdivided into three groups of areas: the supplementary motor areas "SMA proper" (area F3) and "pre-SMA" (area F6) on the mesial cortical surface, the dorsolateral premotor cortex (areas F2 and F7) on the dorsolateral convexity, and the ventrolateral premotor cortex (areas F4 and F5) on the ventrolateral convexity. The primary motor cortex is mainly involved in controlling kinematic and dynamic parameters of voluntary movements, whereas non-primary motor areas are more related to preparing voluntary movements in response to a variety of internal or external cues. Since a structural map of the human isocortical motor system as detailed as in the macaque is not yet available, homologies between the two species have not been firmly established. There is increasing evidence, however, that a similar orga-

nizational principle (i.e., primary motor cortex, supplementary motor areas, dorso- and ventrolateral premotor cortex) also exists in humans. Imaging studies have revealed that functional gradients can be discerned within the human non-primary motor cortex. More rostral cortical regions are active when a motor task is nonroutine, whereas more routine motor actions engage more caudal areas.

Key words Macaque · Homo · Microstructure · Electrophysiology · Functional imaging

Introduction

The agranular frontal cortex of humans and non-human primates has been subdivided into two regions: areas 4 and 6 according to Brodmann (1909) or "precentral area" and "intermediate precentral area" according to Campbell (1905). Area 4 (or "precentral area") is characterized by giant pyramidal or Betz cells in layer V; these cells are missing in area 6 (or "intermediate precentral area"). This simple cytoarchitectonical map corresponded to an equally simple view of functional organization: the "primary motor cortex" (corresponding to Brodmann's area 4) in the precentral gyrus (with a complete representation of body movements), the "supplementary motor area" (Penfield and Welch 1951; Woolsey et al. 1952) on the mesial surface of Brodmann's area 6 (with an additional complete motor representation of the body's periphery; hence the term "supplementary"), and a loosely defined "premotor area" (Fulton 1935) on the lateral cortical convexity. A more elaborate view of the cortical motor system in macaques was proposed by the Vogts, based on a combined myeloarchitectonical and functional study (Vogt and Vogt 1919).

Over recent years, new and more powerful anatomical and functional techniques have shown that this view is no longer adequate: instead of three functional entities, the primate isocortical motor system is made up of many structural and functional fields, each of which processes different aspects of motor behavior.

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Table 1 Synopsis of the various parcellation schemes of the *Macaque* agranular frontal cortex (modified from Schieber 1999)

Generic nomenclature	Generic abbreviation	Brodmann (1909)	Vogt and Vogt (1919)	von Bonin and Bailey (1947)	Barbas and Pandya (1987)	Matelli et al. (1985, 1991)
Primary motor cortex	M1	4	4a, 4b, 4c	FA	4	F1
Dorsocaudal part of the premotor cortex	PMdc	6	6a α	FB	6DC	F2
Supplementary motor area proper	SMA proper					F3
Ventrocandal part of the premotor cortex	PMvc			FBA	6Va	F4
Ventrorostral part of the premotor cortex	PMvr		6b α , 6b β	FCBm	6Vb	F5
Pre-supplementary motor area	Pre-SMA		6a β	FC	MII	F6
Dorsorostral part of the premotor cortex	PMdr				6DR	F7

Similar to the motor cortex, a multiplicity of areas has been defined in the posterior parietal cortex (including the intraparietal sulcus), each of which is involved in the analysis of particular aspects of visual or somatosensory information. Parietal and frontal motor areas are connected in a specific pattern, thus forming several parieto-frontal circuits. These circuits work in parallel and transform different aspects of sensory information into appropriate motor commands.

The aim of this review is to give a concise overview of the anatomical and functional organization of the agranular frontal isocortex in macaques and to discuss possible mechanisms how parietal and frontal areas interact when goal-directed movements are performed. The proisocortical cingulate motor areas will not be dealt with in this review since their structural basis is still poorly established and the maps that have been proposed by various authors in macaques differ from each other in fundamental ways. Some comments on the human cingulate motor areas can be found in Roland and Zilles (1996). We will conclude the article with a discussion of structural and functional aspects of the isocortical motor system in humans.

The structural framework in macaques: microanatomical subdivision of the agranular frontal isocortex

Various architectonical maps of the agranular cortex of the macaque monkey have been published over the past century (Brodmann 1909; Vogt and Vogt 1919; von Bonin and Bailey 1947; Matelli et al. 1985; Barbas and Pandya 1987; Matelli et al. 1991). Most investigators agree that the primary motor cortex is homogeneous, whereas the rostrally adjoining agranular cortex can be subdivided into three groups of areas: the supplementary motor areas "SMA proper" and "pre-SMA" on the mesial cortical surface, the dorsal part of the premotor cortex (PMd) on the dorsolateral convexity, and the ventral part of the premotor cortex (PMv) on the ventrolateral convexity. A synopsis of the various parcellation schemes (Table 1) reveals two aspects.

First, the maps have become more and more complex over time: Brodmann (1909) defined two areas, whereas seven areas can be found in the map by Matelli et al. (1985, 1991). This is certainly due to the more sensitive

techniques that have been used in recent years and that have revealed details that may have been overlooked in previous studies.

Second, the maps vary in terms of size, extent, and topography of cortical areas. This variability very often results from observer-dependent criteria used by different investigators for defining borders between areas. For example, the most widely used criterion for defining the border between Brodmann's areas 4 and 6 is the change in number and density of giant pyramidal (or Betz) cells in layer V. However, these cells do not stop abruptly at the areal border. Instead, their density decreases gradually and there is considerable interindividual variability. If this criterion alone is used, the definition of the area 4/area 6 border becomes more or less arbitrary. This single criterion was used by Barbas and Pandya (1987) for delineating area 6DC (in which giant pyramids are scattered). The mesial part of area 6DC, however, is the leg representation of the SMA proper (see below; Mitz and Wise 1987; Luppino et al. 1991, 1993) and cannot be considered as a functionally independent field. On the other hand, when areas are defined on the basis of a combination of (1) different criteria and (2) different technical approaches, their location and extent becomes

Fig. 1 Mesial (A) and lateral (C) views of the macaque brain showing the areas of the agranular frontal cortex according to Matelli et al. (1985, 1991) and of the posterior parietal cortex according to Pandya and Seltzer (1982) with the somatotopic representations of the body. The areas lying within the intraparietal sulcus (*IP*) are defined according to electrophysiological data (see text) and are depicted in an unfolded view of the sulcus (B *upper half* medial bank, *lower half* lateral bank, *dashed line* fundus of the sulcus). Lateral views of the human brain (D, E) showing the map of the agranular frontal cortex according to Vogt and Vogt (1919) and Foerster (1936) with the somatotopic representations of the body (D) and the suggested homologies with the macaque cortex (E). Identical colors in C and E indicate areas and sulci considered to be homologous. See text for further details. (8 Brodmann's area 8 (frontal eye field), *AG* annectant gyrus, *AI* inferior arcuate sulcus, *AS* superior arcuate sulcus, *C* central sulcus, *Ca* calcarine sulcus, *Cg* cingulate sulcus, *FEF* frontal eye field, *IF* inferior frontal sulcus, *IFG* inferior frontal gyrus, *IO* inferior occipital sulcus, *IP* intraparietal sulcus, *IPa* inferior precentral sulcus (ascending branch), *IPD* inferior precentral dimple, *IPd* inferior precentral sulcus (descending branch), *L* lateral sulcus, *Lu* lunate sulcus, *MFG* middle frontal gyrus, *OT* occipitotemporal sulcus, *P* principal sulcus, *POs* parieto-occipital sulcus, *S* spur of the arcuate sulcus, *SF* superior frontal sulcus, *SFG* superior frontal gyrus, *SP* superior precentral sulcus, *SPD* superior precentral dimple, *ST* superior temporal sulcus.) Modified from Rizzolatti et al. 1998. Reprinted with permission from Elsevier Science

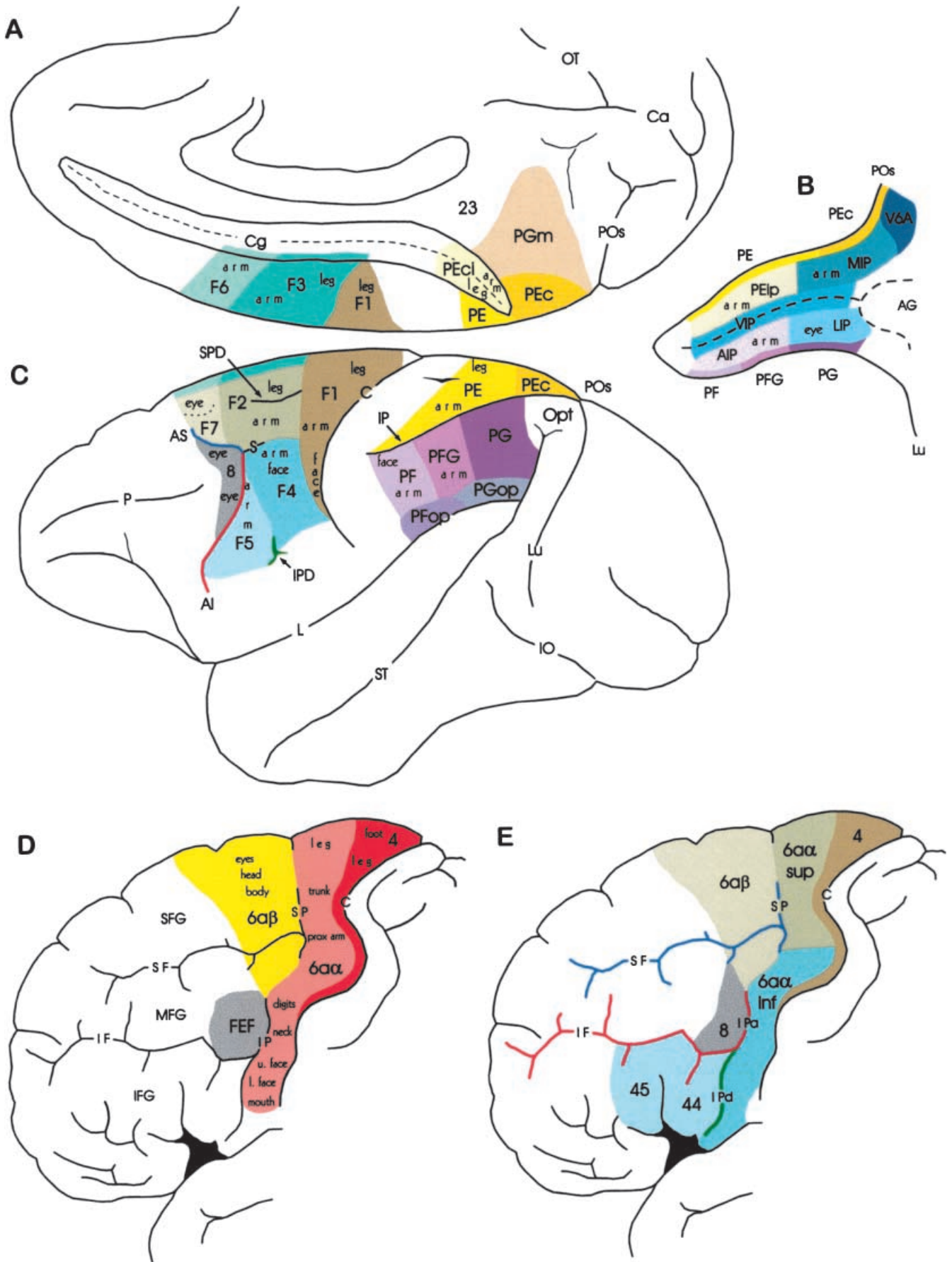
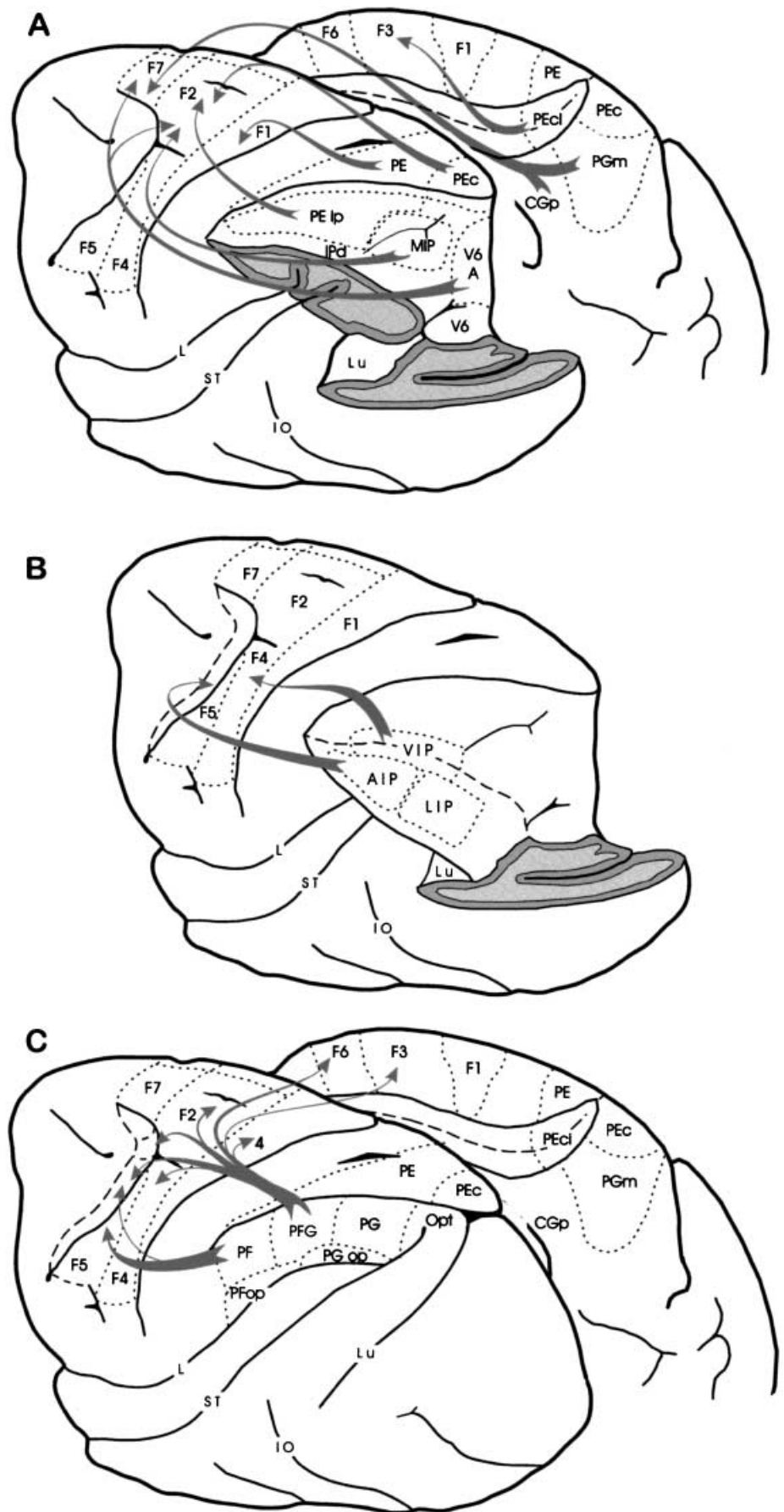


Fig. 2A–C Parieto-frontal circuits in the macaque monkey. Parietal projections originating from the mesial parietal cortex, free surface of the superior parietal lobule, and medial bank of the intraparietal sulcus are shown in **A** (inferior parietal lobule and occipital lobe removed), from the fundus and lateral bank of the intraparietal sulcus in **B** (intraparietal sulcus opened (dashed line indicates fundus) and occipital lobe removed), and from the free surface of the inferior parietal lobule in **C**. For other conventions see Fig. 1. Reprinted from Rizzolatti et al. (1998) with permission from Elsevier Science



more reliable and they indeed reflect structurally and functionally different entities. The “F” nomenclature of Matelli et al. (cf. Table 1, last column) that is used throughout this article was introduced in 1985 based on regional differences in cytochrome oxidase histochemistry. The terminology was adopted for two reasons. First, the location of the enzymatic areas was very similar to that of the cytoarchitectonic areas of von Bonin and Bailey (1947), hence a terminology similar to theirs (“F” for frontal cortex; instead of capital letters for each area (FA, FB, etc.), as introduced by von Bonin and Bailey, the areas were numbered in a caudo-rostral sequence). Second, the authors wanted to avoid functional terms such as M1, supplementary motor area, etc. (see also Matelli et al. 1985). Ever since, this parcellation has been confirmed with other techniques, such as cytoarchitecture (Matelli et al. 1991), receptor autoradiographic mapping of the binding sites of classical neurotransmitters (Zilles et al. 1995; Geyer et al. 1998a), and, most recently, the immunohistochemical staining of neurofilament proteins with the monoclonal antibody SMI-32 (Matelli et al. 1996; Geyer et al. 1998b; Gabernet et al. 1999; Geyer et al. 2000; Petrides et al. 2000). For example, areas F3 and F6 according to this nomenclature correspond to two different functional entities (SMA proper and pre-SMA, respectively; see Tanji 1994; Rizzolatti et al. 1996a).

Areas F1 to F7 represent the agranular frontal isocortex (Fig. 1A,C). Its caudal border (towards the primary somatosensory cortex) lies close to the fundus of the central sulcus and its mesial border (towards the cingulate cortex) in the upper bank of the cingulate sulcus. Its rostral border (towards the prefrontal cortex) lies close to the fundus of the arcuate sulcus and looks like a mirrored “c”. Only its lateral border on the cortical convexity does not coincide with a macroanatomical landmark. It runs approximately from the lateral end of the inferior arcuate sulcus to the lateral end of the central sulcus. Area F1 corresponds to the primary motor cortex. Areas F2 to F7 lie further rostrally: areas F3 and F6 on the mesial cortical surface, areas F2 and F7 on the dorsolateral cortical convexity (between the midline and the level of the spur of the arcuate sulcus), and areas F4 and F5 on the ventrolateral convexity (between the spur of the arcuate sulcus and the lateral border of the agranular frontal cortex).

The organizational principle: parieto-frontal circuits

As already stated in the introduction, a multiplicity of areas has also been defined in the posterior parietal cortex. Anatomically the posterior parietal cortex is formed by two lobules, separated by the intraparietal sulcus: the superior parietal lobule (SPL) and the inferior parietal lobule (IPL). A map of the SPL and IPL is shown in Fig. 1C. The SPL and IPL receive somatosensory and visual inputs. The caudal areas of both the SPL and IPL process mainly visual information, whereas the rostral areas are related to somatosensory input in the SPL and to an integration of somatosensory and visual inputs in the

IPL (Rizzolatti et al. 1998). Posterior parietal and frontal areas are connected in a specific way. Each frontal area receives afferents from a specific group of posterior parietal areas, the input from one parietal area being rich (“predominant” input) and from the other areas of the group being moderate or weak (“additional” inputs). Conversely, each posterior parietal area projects to a group of frontal areas, again the output to one frontal area being rich (“predominant” output) and to the other areas of the group being moderate or weak (“additional” outputs). The “predominant” connections between the posterior parietal and frontal areas are summarized in Fig. 2A–C. Parietal and frontal areas linked by “predominant” connections have similar functional properties. They constitute several parieto-frontal circuits working in parallel and being involved in specific sensory-motor transformations for goal-directed actions. These circuits are important functional units of the cortical motor system (Rizzolatti et al. 1998).

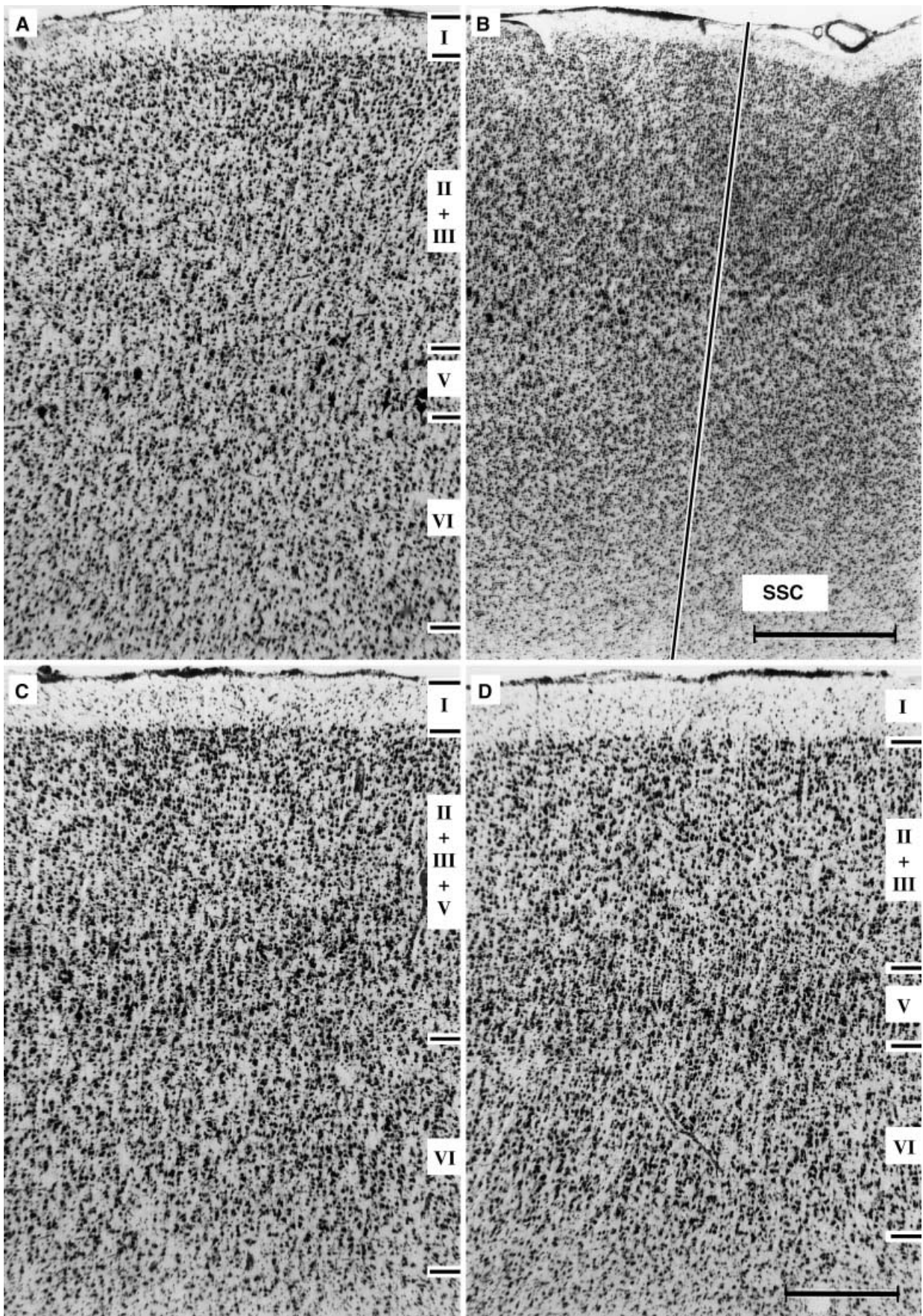
The isocortical motor system in macaques

As this review focuses on the agranular frontal isocortex, the functional units will be described in the following sequence: primary motor cortex (area F1), SMA proper and pre-SMA on the mesial cortical surface (areas F3 and F6, respectively), the PMd on the dorsolateral convexity (areas F2 and F7), and the PMv on the ventrolateral convexity (areas F4 and F5).

Primary motor cortex (area F1)

Microstructure

Cytoarchitectonically area F1 is characterized by low cell density, poor lamination, absent layer IV, and very prominent giant pyramidal cells in layer V (Fig. 3A). Several easily visible criteria differentiate area F1 from the primary somatosensory cortex which shows an increasing cell density, an emerging inner granular layer (layer IV), and a lack of giant pyramidal cells (Fig. 3B). On the lateral convexity, the border between area F1 and the somatosensory cortex lies close to the fundus of the central sulcus. The rostral border of area F1 (towards areas F3, F2, and F4) is much more difficult to define since the cytoarchitectonic features do not change abruptly but rather merge gradually. The giant pyramidal cells also decrease gradually in density and there is considerable interindividual variability. A more recent technique, the immunohistochemical staining of non-phosphorylated epitopes on the neurofilament protein triplet with the monoclonal antibody SMI-32 (Sternberger Monoclonals, Baltimore, USA; Sternberger and Sternberger 1983; Lee et al. 1988) labels a subset of pyramidal neurons with highly specific regional and laminar distribution patterns (Fig. 4). Neurofilament proteins are involved in the maintenance and stabilization of the cytoskeleton of the axon. Their immunohistochemical



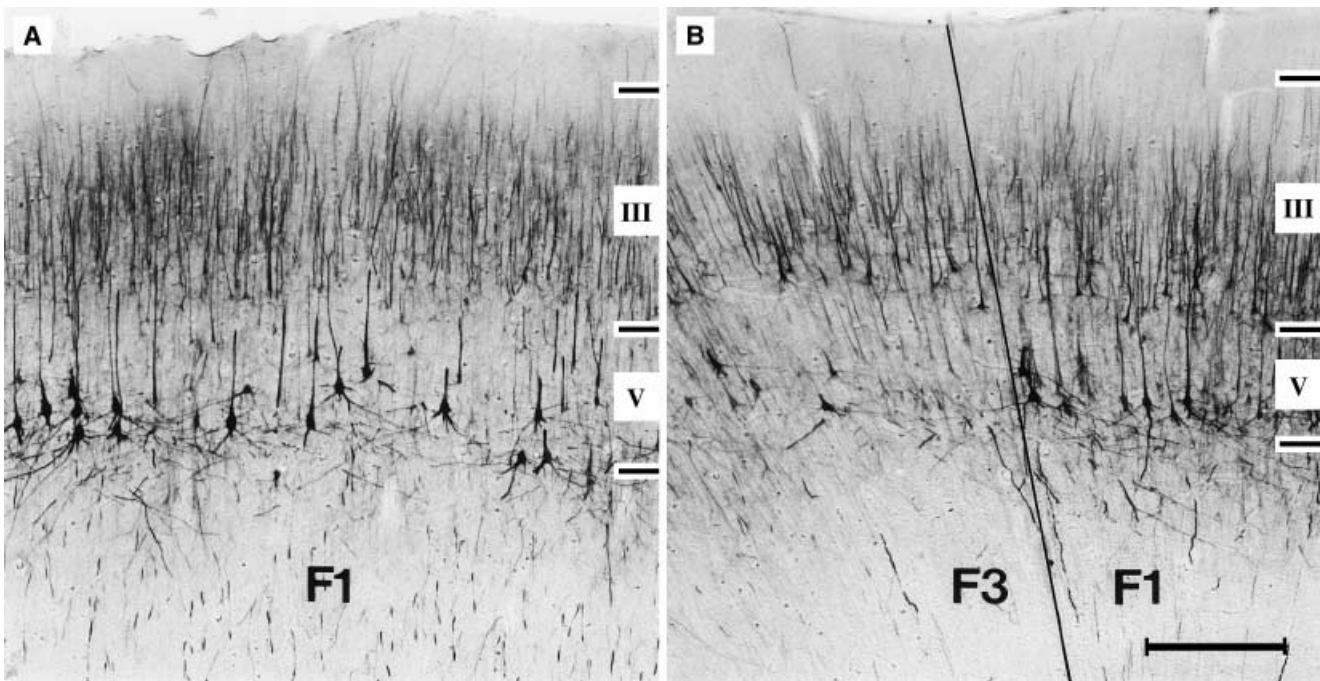


Fig. 4 SMI-32 immunoarchitecture of area F1 (A) and the border between areas F1 and F3 (B). In area F1, pyramidal cells in layers III and V and giant pyramids (or Betz cells) in layer V are immunoreactive. A sharp drop in immunoreactivity marks the border between areas F1 and F3. *Roman numerals* indicate cortical layers. *Bar* 500 μm (A,B)

detection in the soma has been correlated with neuronal and axonal size and with the conduction velocity of nerve fibres. For example, the percentage of neurofilament protein-immunoreactive pyramidal neurons is low (typically less than 50%) in short corticocortical pathways and high (typically more than 50%) in long association pathways (Hof et al. 1995). Since only a subset of pyramidal neurons is immunostained, it is easier to differentiate cortical areas in this “simplified” view of cortical architectonics. With SMI-32 immunohistochemistry, the rostral border of area F1 (Fig. 4B) can be defined more precisely, e.g., by changes in the immunoreactivity of layers III and V (Geyer et al. 1998b; Gabernet et al. 1999; Geyer et al. 2000). The rostral border of area F1 lies on the exposed cortical surface (Fig. 1C). Close to the midline, area F1 may reach up to the level of the caudal end of the superior precentral dimple. Further laterally, its rostral border recedes caudally and eventually disappears in the rostral bank of the central sulcus. A small sector of area F1 occupies the mesial cortical surface

(Fig. 1A). The ventral border lies in the upper bank of the cingulate sulcus.

All these data point to a microstructural homogeneity of area F1. Some years ago a subdivision of the primary motor cortex (except for the face region) into a rostral (area M1r) and a caudal (area M1c) band running medio-laterally parallel to each other was proposed in the New World owl monkey (*Aotus trivirgatus*; Stepniewska et al. 1993). Differences in cytoarchitecture (layer V pyramids are smaller in M1r than in M1c), connectivity (M1r is connected mainly with the non-primary motor and somatosensory cortex, M1c only with the somatosensory cortex), and electrophysiological properties (thresholds for eliciting movements with intracortical microstimulation are higher on average in M1r than in M1c) indicate a differential involvement of the two subdivisions in the control of different motor activities. It was argued that M1r may be preferentially involved in the early stages of a movement including postural adjustments to maintain balance, in reaching towards an object, and in pre-shaping the fingers to accommodate the object. M1c may be mainly involved in the later stages of a movement (when cutaneous and kinesthetic feedback is crucial) including the fine adjustments of the fingers (Stepniewska et al. 1993). A similar subdivision of the primary motor cortex has been shown in humans (see below) but not in Old World macaque monkeys.

Connectivity

Although area F1 does not have an inner granular layer (layer IV) this does not mean that area F1 does not receive thalamic afferents. The rostral part of area F1 receives its main thalamic input from the nucleus ventralis lateralis pars oralis (VLo), plus smaller contributions

◀ **Fig. 3** Cytoarchitecture of area F1 (A), the border between area F1 and the primary somatosensory cortex (SSC; B), areas F3 (C), and F6 (D). In a caudo-rostral direction (from area F1 to area F6), the cellular density in layers III and V increases and the cortical layers stand out more clearly. In the SSC, an inner granular layer (layer IV) emerges. *Roman numerals* indicate cortical layers. *Bars* 500 μm (A, C–D) and 1 mm (B). A and C–D reprinted from Geyer et al. (1998a) with permission from John Wiley & Sons

from the nucleus ventralis posterolateralis pars oralis (VPLo), and the nucleus ventralis lateralis pars caudalis (VLc). The caudal part of area F1 is innervated mainly from the nucleus VPLo, plus a small contribution from the nucleus VLo (Matelli et al. 1989). Thalamocortical terminals are present in all layers of area F1, being densest in lamina III and the deep part of lamina V (Strick and Sterling 1974; Sloper and Powell 1979).

Corticocortical afferents to the F1 hand area are dominated by those from the SMA, followed by the lateral premotor cortex, and areas 1, 2, and 5 (Ghosh et al. 1987). Callosal afferents originate from pyramidal cells in lower lamina III in the homotopic part of contralateral area F1 and terminate in laminae I-III (Sloper and Powell 1979). Callosal connections between the representations of the most distal parts of the arms and legs have not been described (Jones and Powell 1969; Gould et al. 1986).

Subcortical projections of area F1 originate from pyramidal cells in lamina V (except for some corticostriate fibers that arise from lamina III and most corticothalamic fibers that arise from lamina VI (Goldman-Rakic and Selemon 1986)). Within lamina V there is a superficial-to-deep layering of neurons that project to the striatum, midbrain, brain stem, and spinal cord, respectively (Jones and Wise 1977).

In addition to differences in their laminar origin, descending motor projections also originate from different regions of the sensorimotor cortex. In contrast to older studies (Holmes and May 1909) it is now clear that the corticospinal tract originates not only from area F1. Instead, there are substantial projections from other frontal and parietal areas. Studies based on fiber degeneration (Russel and DeMeyer 1961) and the distribution of retrogradely labelled neurons after injections of horseradish peroxidase (HRP; Murray and Coulter 1981; Toyoshima and Sakai 1982) have shown that 40–60% of the corticospinal fibers originate from the frontal lobe (30–50% from area 4 and 10–30% from area 6) whereas the remaining 40–60% originate from the parietal lobe [according to one study (Toyoshima and Sakai 1982): 13% from areas 3, 1, and 2, 12% from area 5, and 12% from the second somatosensory cortex = in total 37% from the parietal lobe]. In a more recent study HRP conjugated with wheat germ agglutinin was injected into the lower cervical spinal cord and the distribution of corticospinal neurons was studied in the frontal lobe. 50% of the labeled cells were found in the primary motor cortex, 15–20% in the cingulate motor areas, 10–20% in the SMA, and 10–20% in the lateral premotor cortex (Dum and Strick 1991).

When considering the descending pathways, the motor capacity of an animal (e.g., manual dexterity) is not so much influenced by the location of their cells of origin as by the interneurons and motoneurons on which these pathways terminate (Kuypers 1973). Based on the spinal level to which the corticospinal tract penetrated and on differential projections of the tract to different parts of the spinal grey matter, Kuypers (1981) divided mammalian species into four groups. Group 1 (ungulates, the rabbit,

and most of the marsupials) are mammals with corticospinal fibers extending only to cervical or mid-thoracic segments and terminating in the dorsal horn. Group 2 (carnivores, the rat, some New World monkeys) are mammals with corticospinal fibers extending throughout the spinal cord and terminating in the dorsal horn and intermediate zone. Direct cortico-motoneuronal (CM) connections are absent or sparse. Group 3 (most of the New and Old World monkeys) have corticospinal fibers extending throughout the spinal cord and terminating in the dorsal horn, intermediate zone, and dorsolateral groups of the lateral motoneurons. Direct CM projections exist to the dorsolateral groups of the lateral motoneurons that innervate the muscles of the upper and lower extremities. Group 4 (man and the great apes) have corticospinal fibers extending throughout the spinal cord and terminating in the dorsal horn, intermediate zone, and both dorsolateral and ventromedial groups of the lateral motoneurons. Direct CM projections exist to the dorsolateral (innervating the distal muscles of the extremities) and ventromedial (innervating more proximal and axial muscles) groups of the lateral motoneurons. Heffner and Masterton (1975, 1983) introduced an index of digital dexterity for different mammals based on whether the distal upper extremity is used only for locomotion (i.e., restrained digits or separate digits that do not converge when flexed), as a primitive hand (i.e., convergent but not prehensile digits), or whether it is specialized for manipulation (i.e., prehensile digits without or with an opposable thumb capable of only a power or a precision grip). They found that only the spinal level to which the corticospinal tract penetrated and the presence of CM projections (but not other factors, e.g., fiber number of the corticospinal tract, mean fiber diameter, or the size of the largest fibers) are strongly correlated with the dexterity index in different species. CM projections are far more numerous in man and the great apes than in the macaque (Kuypers 1981) and it seems that the CM connections are crucially important for independent finger movements (Bernhard et al. 1953; Kuypers 1962).

Function

Area F1 is organized somatotopically. On the cortical convexity, the face is represented laterally close to the Sylvian fissure, the leg medially close to the midline (also extending on the mesial wall of the hemisphere), and the arm in between (Fig. 1A,C). Proximal parts of the extremities and axial body parts are primarily represented on the exposed cortical surface, whereas distal parts of the extremities and acral parts of the face (lips and tongue) are mainly represented in the rostral bank of the central sulcus (Woolsey et al. 1952). Those parts of the body that are used for fine movements (fingers, lips, tongue) are represented over a larger cortical territory than are body parts that are used in coarser movements (trunk, proximal extremities). By accordingly distorting the proportions of the body parts, Woolsey (1952) gener-

ated the cartoon of the so-called “motor simiusculus”, the monkey equivalent of the more famous “motor homunculus” by Penfield (Penfield and Rasmussen 1952). Somatotopic organization, however, should not be overinterpreted. Somatotopy means an orderly representation of the body’s periphery; it does not mean a one-to-one map of individual muscles, joints or movements. Both hand and arm muscles (Donoghue et al. 1992) and finger movements (Schieber and Hibbard 1993) are represented as overlapping and *not* as somatotopically segregated neuronal populations, thus indicating a higher order representation that lies beyond the simple muscle or joint level (see also Poliakov and Schieber 1999). Intracortical microstimulation reveals that individual muscles are typically activated at multiple, spatially separated locations and usually more than one muscle is activated from a single site (Donoghue et al. 1992). There is *convergence of outputs* on the one hand, i.e., the outputs from a large F1 territory converge on the spinal motor neuron pool that controls muscles moving a given body part. On the other hand, there is *divergence of outputs*, i.e., the outputs from single F1 neurons ramify and synapse on multiple spinal neuron pools. The latter principle has also been confirmed anatomically. Intracellular staining has shown that a single physiologically identified corticospinal axon branches extensively within the spinal cord and terminates within the motor neuron pools of many muscles (Shinoda et al. 1981).

What does area F1 contribute to motor control? In the 1960s Evarts started to extracellularly record the electrical activity from area F1 pyramidal tract neurons in awake and behaving monkeys. In one of these experiments the monkeys were trained to raise and lower weights with flexion and extension movements of the wrist (Evarts 1968). Flexion- and extension-related neurons could be differentiated. A typical flexion-related neuron would begin to discharge as early as several hundred milliseconds before flexion onset, increase its firing rate when the beginning of the movement approached, and fire with maximal intensity during flexion. During extension, the same neuron fired with considerably lower frequency or was silent altogether. An extension-related neuron would behave in the opposite way. In subsequent studies, it could be shown that the discharge frequencies of pyramidal tract neurons were related to a number of mechanical parameters of the movements the animals were performing, e.g., the force the monkeys had to exert, the rate of change of force, the joint position, or the velocity of the movement, whereby single neurons often encoded several of these parameters. Thus, it seems that area F1 neurons control kinematic and dynamic parameters of movement, whereas motor-related areas other than F1 seem to use external (e.g., sensory) or internal cues to trigger and guide movements (see below).

Given the fact that area F1 neurons are fairly broadly tuned in terms of movement parameters, how then can we make precise movements, e.g., when reaching to a target in space? This issue was addressed by Georgopoulos and colleagues who trained monkeys to move their hand

and arm from the center of a circle towards a small light whose position varied randomly around a circle (Georgopoulos et al. 1982). The area F1 cells fired maximally during movement in one direction (so-called preferred direction), but also (though less vigorously) during movements that deviated clockwise or counterclockwise from the preferred direction. Each neuron’s directional tuning curve resembled the shape of a Gaussian distribution curve with the curve’s peak representing the neuron’s preferred direction. Such a coarse tuning at the single neuron level could not explain the precise movements the monkey was performing in space. However, Georgopoulos recorded not only from one cell but from more than 200 area F1 neurons and established a tuning curve and a *direction vector* for each neuron. A neuron that fired most vigorously during a movement, say, to the left was represented by a direction vector pointing to the left. For a movement in any other direction, the same neuron’s direction vector pointed to the left as well, but the length of the vector decreased proportionally to the decrease in the neuron’s firing rate. For each direction of movement, all single direction vectors were plotted together and averaged to yield a so-called *population vector* for this movement direction. Most interestingly, for each movement direction, an excellent agreement was found between the direction of the actual movement the monkey was making and the direction of the population vector.

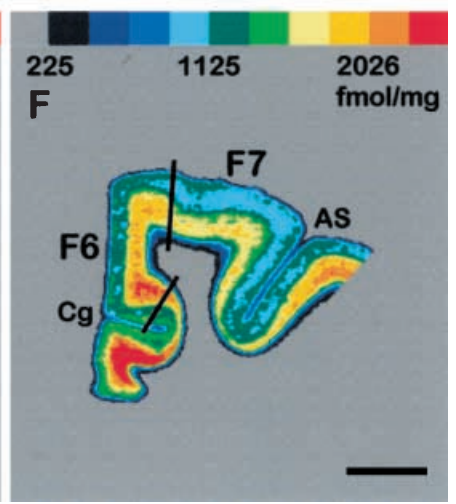
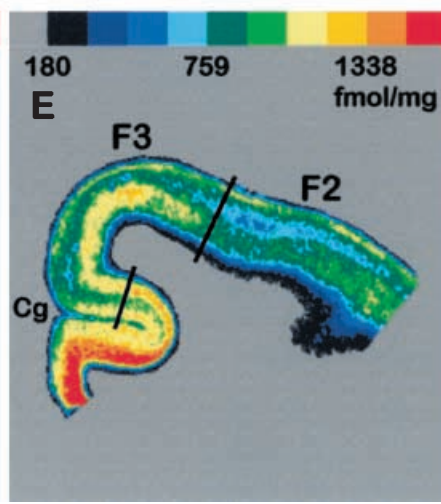
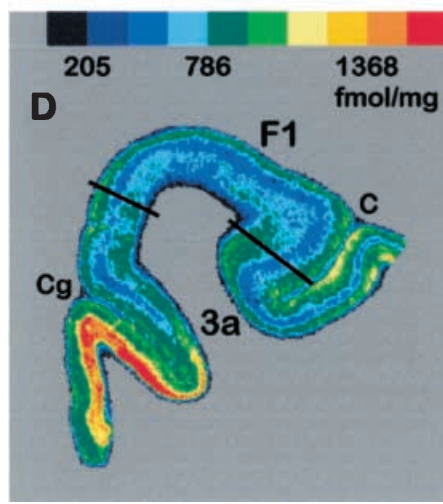
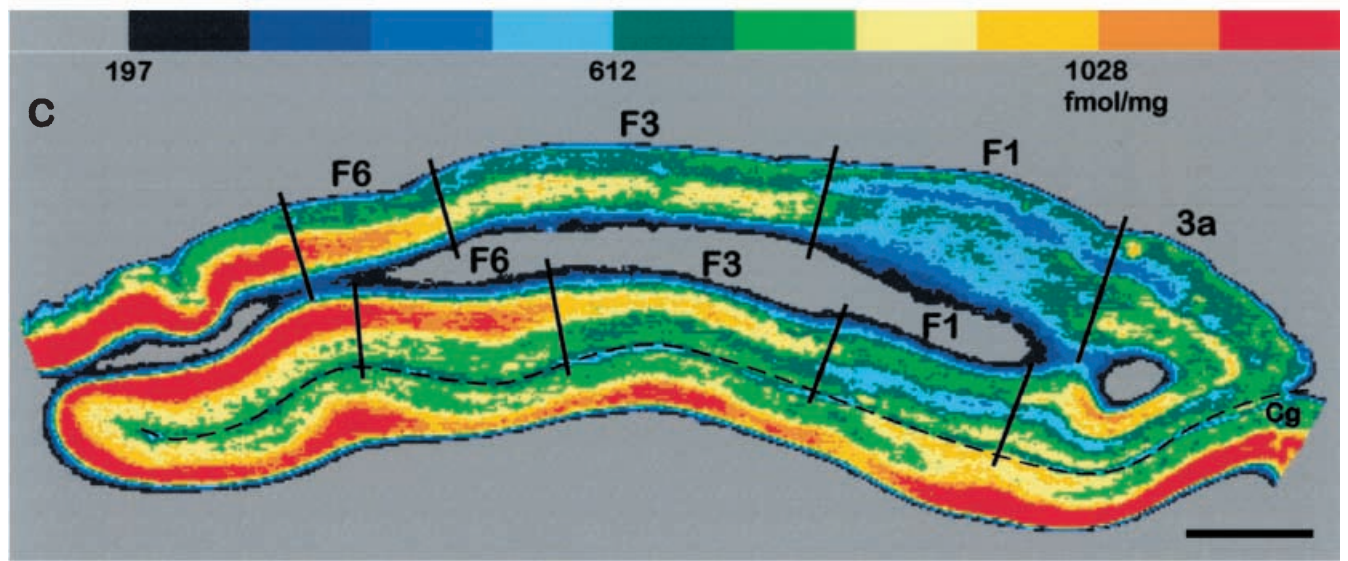
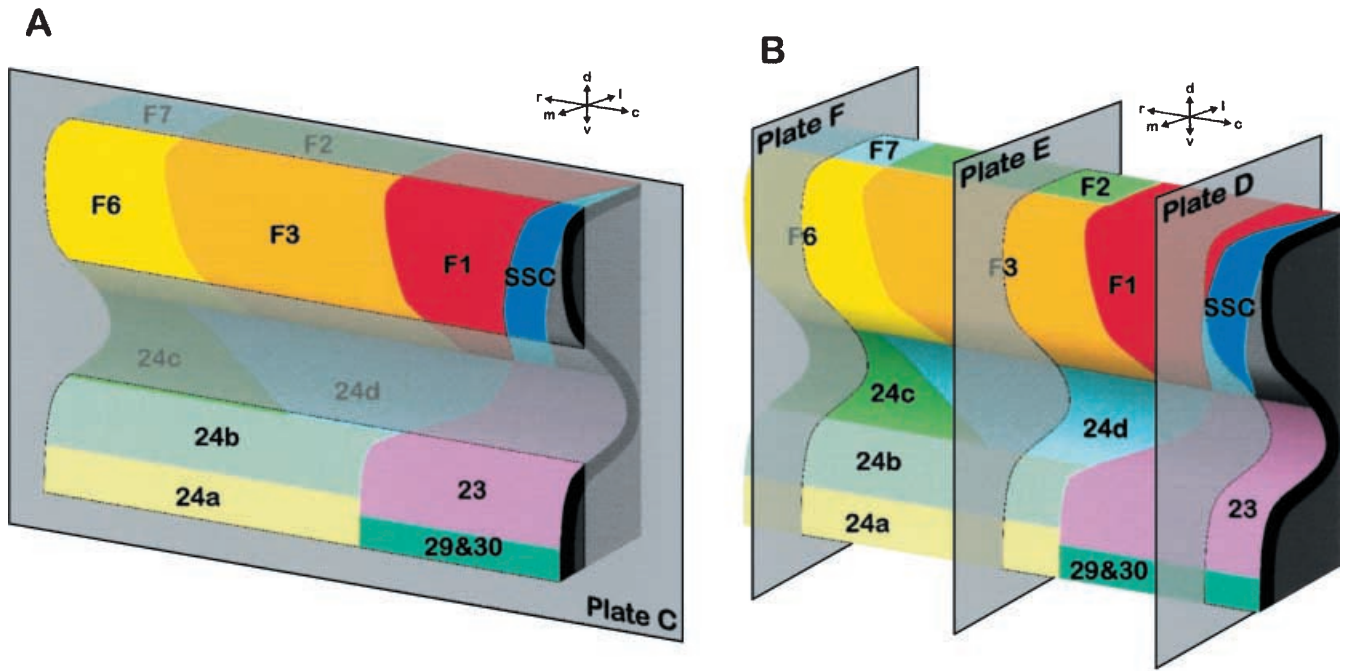
This work suggests three important conclusions about how area F1 commands voluntary movements: (1) much of the motor cortex is active for every movement, (2) the activity of each cell represents a single “vote” for a particular direction of movement, and (3) the direction of movement is determined by a tally (and averaging) of the votes registered by each cell in the population (Bear et al. 1996).

Supplementary motor areas “SMA proper” and “pre-SMA” (areas F3 and F6)

Microstructure

The term “supplementary motor area” (SMA) was introduced by Woolsey and co-workers. Electrical stimulation of the monkey cortex revealed a complete somatotopic map of the body in the primary motor cortex (“motor simiusculus”; see above) and an additional (or “supplementary”) complete motor representation further rostrally on the mesial cortical surface (Woolsey et al. 1952). For a long time the SMA was considered a homogeneous entity. However, over recent years it has become clear that the SMA in fact corresponds to two areas that differ from each other both in terms of microstructure and function, namely the SMA proper (or area F3) and the pre-SMA (or area F6).

From a historical perspective, the concept that the non-primary motor cortex on the mesial surface is not homogeneous is not new. The Vogts (Vogt and Vogt



1919) subdivided it into areas 6 α and 6 β , von Bonin and Bailey (1947) into areas FB and FC, and Barbas and Pandya (1987) into areas 6DC and MII (cf. Table 1). However, the different maps vary considerably in terms of size and rostro-caudal extent of the areas. In addition, most of these areas extend from the mesial surface further laterally on the dorsolateral convexity up to the level of the superior branch and spur of the arcuate sulcus. The functional properties of neurons on the dorsolateral convexity, however, are markedly different from those on the mesial cortical surface, a fact that is not taken into account by these maps.

The parcellation of the mesial cortex into areas F3 and F6 is based on histochemical (Matelli et al. 1985), cytoarchitectonic (Matelli et al. 1991), and most recently receptor autoradiographic (Fig. 5; Geyer et al. 1998a) data. Clear-cut changes in the staining pattern of cytochrome oxidase and in the laminar binding patterns especially of glutamate (revealed with [³H] α -amino-3-hydroxy-5-methyl-4-isoxalone propionic acid (AMPA) and [³H]kainate; Fig. 5C–F) and muscarinic cholinergic (revealed with [³H]oxotremorine-M) binding sites very closely match corresponding cytoarchitectonic borders. In Nissl-stained sections, area F3 is poorly laminated like area F1 (Fig. 3C). The most distinguishing feature from area F1 is an increase in cellular density in lower layer III and upper layer V. Scattered giant pyramidal cells are present only in the caudal part of area F3 towards the border to F1. Unlike areas F1 and F3, area F6 is clearly laminated (Fig. 3D). Its most prominent feature is a dark layer V well demarcated from layers III and VI. At the rostral border of area F6 an incipient layer IV becomes evident. Area F3 lies on the mesial cortical surface immediately rostral to area F1 and extends for 8 to 10 mm in the rostrocaudal direction (Fig. 1A). Area F6 lies anterior to area F3. It has a common border with area F3 and extends rostrally for 5 to 6 mm up to the granular prefrontal cortex. No macroanatomical landmarks indicate the borders between areas F1 and F3, F3 and F6, and F6 and the prefrontal cortex. Areas F3 and F6 abut on the cingulate cortex approximately in the middle of the dorsal bank of the cingulate sulcus and extend on the dorsolateral convexity for approximately 2 to 3 mm (Fig. 1C; Matelli et al. 1991; Geyer et al. 1998a).

◀ **Fig. 5** Schematic drawings of the mesial cortical surface depicting the planes of sectioning as shown in plate C (A) and in plates D, E, and F (B). The cingulate sulcus is opened to expose the extent of areas in its dorsal and ventral bank. Contrast-enhanced and color-coded autoradiographs showing the distribution patterns of [³H]kainate binding sites in a paramedian section (C) and in a series of coronal sections from three different caudo-rostral levels (D–F). Blue pixels indicate low densities of binding sites, red pixels indicate high densities (cf. color bar). B_{\max} values are expressed as fmol/mg protein. Changes in the laminar distribution patterns of binding sites that coincide with cytoarchitectonically defined borders in adjacent cell-stained sections are marked. (23, 24a, 24b, 24c, 24d, 29&30, areas of the cingulate cortex (see also Matelli et al. 1991); 3a primary somatosensory area 3a, SSC primary somatosensory cortex, *r* rostral, *c* caudal, *m* medial, *l* lateral, *d* dorsal, *v* ventral. For other abbreviations see Fig. 1). Bars 5 mm (C, D–F). C–F reprinted from Geyer et al. (1998a) with permission from John Wiley & Sons

Connectivity

The different functional roles of areas F3 and F6 in motor control are further substantiated by their different input and output properties. Area F3 receives its main thalamic input from the nucleus ventralis lateralis pars oralis (VLo), whereas the input to area F6 comes mostly from the nucleus ventralis anterior pars parvocellularis (VApc), area X of Olszewski (1952), and the nucleus medialis dorsalis (Matelli and Luppino 1996; Rizzolatti et al. 1996a). Both areas are elements of different sub-cortical motor loops. Area F3 is the target (via the nucleus VLo) of the putamen and pallidum whereas area F6 receives its input (via the nucleus VApc) from the caudate (Alexander et al. 1986) and the cerebellum (Rouiller et al. 1994).

Cortical afferents to area F3 originate predominantly from areas F2 and F4 (~25%), areas F5, F6, and F7 (~20%), the primary and secondary somatosensory cortex, and the posterior parietal areas PE and PEci (Figs. 1A and C; ~20%), the cingulate cortex (~20%), and the primary motor area F1 (~15%). Area F6 is mainly connected with areas F5 and F7 (~40%), the prefrontal cortex (~20%), the cingulate cortex (~20%), areas F2, F3, and F4 (~15%), and the posterior parietal areas PG, PFG, and the superior temporal sulcus (Fig. 1C; ~5%). In contrast to area F3, F6 is *not* connected with area F1 (Luppino et al. 1993; Rizzolatti et al. 1996a).

Descending projections from area F3 are corticospinal and corticobulbar in nature. The caudal part of area F3 projects to the thoracolumbar segments and the rostral part to the cervicothoracic segments of the spinal cord. Only corticobulbar projections originate from area F6 (Keizer and Kuypers 1989; Luppino et al. 1994; He et al. 1995; Rizzolatti et al. 1996a).

Function

Area F3 is somatotopically organized. The arm and leg representations are two oblique bands running in a dorsorostral-to-ventrocaudal direction. The arm is represented in the rostral, the leg in the caudal band (Fig. 1A). A small orofacial representation is located even further rostrally at the border to area F6. Area F6 contains only a representation of the arm (Luppino et al. 1991).

Intracortical microstimulation (ICMS) experiments revealed marked differences between the movements evoked from mesial area F1, area F3, and area F6. Almost all stimulation sites (99%) in mesial area F1 are excitable with standard ICMS procedures. Movements can be evoked at low thresholds (on average <20 μ A) and are typically fast and short-lasting in nature. Most movements (~90%) are simple movements (i.e., restricted to a single joint or the digits of one extremity), whereas only ~10% of the induced movements are contiguous movements (i.e., displacements occurring at two adjacent joints) or complex movements (i.e., displacements of more than two articulations or of noncontiguous articula-

tions or body parts, e.g., shoulder and wrist). Proximal and distal movements are equally well represented and are spatially clearly segregated. In contrast, in area F3 only ~80% of the stimulation sites are excitable with standard ICMS procedures. The evoked movements are typically fast and short-lasting as well but movement thresholds are higher (on average 10–30 μA) than in area F1. The nature of the induced movements is also somewhat different from mesial area F1. In area F3 only ~60% are simple movements (vs. ~90% in mesial F1), whereas ~30% are complex movements (vs. ~5% in mesial F1). Proximal movements are much more represented in area F3 than are distal movements and they are spatially poorly separated. Finally, in area F6, only ~20% of the stimulation sites are excitable with standard ICMS procedures and the movement thresholds are even higher (on average 20–40 μA) than in area F3. Sixty percent of the induced movements are fast and short-lasting, whereas 40% are slow displacements of the limbs that somewhat mimic natural movements or postural adjustments of the animal. (This latter type of movements cannot be evoked from area F3 or mesial area F1.) In area F6, proximal movements are also much more represented than are distal movements and spatial separation is also poor (Luppino et al. 1991). To sum up, the ICMS data show that from mesial area F1 to area F6 cortical excitability decreases whereas the thresholds at which movements can be elicited and the degree of complexity of the induced movements increase.

What does the SMA (SMA proper and pre-SMA) contribute to motor control? Traditionally it was thought that the SMA is more involved in the control of complex (versus simple) motor tasks, in the internal (versus external) initiation of motor acts, and in controlling proximal (versus distal) limb movements. A recent review on “new concepts of the supplementary motor area” (Tanji 1996) however concluded that the SMA influences many aspects of motor behavior and any over-simplification of the “function” of the SMA is no longer appropriate. The main concepts are briefly summarized here (cf. Tanji 1994; Tanji 1996).

Complex versus simple motor tasks What does “simple” or “complex” mean? “Simple” does not necessarily mean “smallness of the body part involved in the movement”. It is by no means “simple” to move one finger without moving others since this involves active suppression of many finger muscles. Nor is a movement, even if it is apparently easy to execute, “simple” if it must be selected according to complex rules. “Simple” in this context means performing a “kind of motor task that does not include a temporal or spatial structure imposing a great deal of specific requirements for the subjects” (Tanji 1994). Neuronal activity in the SMA changes before and during execution of “simple” movements (Brinkman and Porter 1979; Tanji and Kurata 1979, 1982; Okano and Tanji 1987; Romo and Schultz 1987; Thaler et al. 1988). On the other hand, the effects of unilateral or bilateral lesions of the SMA appear surprisingly mild at first

glance. No gross motor deficits were observed. The animals were able to run, climb, and grasp food without major difficulties (Brinkman 1984; Passingham et al. 1989). However, subtle effects became evident when the monkeys performed more complex hand movements. Brinkman (1984) observed a transient clumsiness when food was retrieved unimanually with relatively independent finger movements and a long-lasting failure in bimanual coordination (the two hands tended to behave in a similar manner instead of sharing the task between them). Halsband (1982) noted that after an SMA lesion the monkeys could not perform a sequence of three movements with a manipulandum. Thus, the old concept is no longer appropriate since the SMA is involved in both “simple” and “complex” motor tasks.

Internal versus external motor initiation What is “internal” and what is “external” initiation of movements? Passingham (1993) gives a simple yet very graphic example. “Consider a dog lying on the floor. It comes when its master calls; but there are other occasions on which it gets up and comes of its own accord. In the first case there is a change in the environment: it hears the call. In the second case there is no change in the environment: instead there is a change in the animal itself. In one instance the animal reacts to an external event, and in the other its action is self-initiated. We may say that the individual ‘acts’”. A traditional concept has been that the SMA is involved in self-initiated or internally guided movements, whereas the lateral premotor cortex is involved in movements triggered or guided by sensory signals (Eccles 1982; Rizzolatti et al. 1983; Goldberg 1985; Tanji 1994). Subsequent electrophysiological studies, however, have shown that neurons both in the SMA and the lateral premotor cortex are active no matter whether monkeys performed self-initiated (“internal”) or externally guided (“external”) movements (Okano and Tanji 1987; Romo and Schultz 1987; Thaler et al. 1988; Kurata and Wise 1988). There is no simple dichotomy in function between the SMA and the lateral premotor cortex (at most there is a *relative* importance of the SMA in self-initiated and the lateral premotor cortex in externally guided movements). Recent studies have confirmed this concept: the SMA is involved both in externally guided, e.g., visually triggered motor tasks (Grafton et al. 1996) and in self-initiated motor acts, e.g., in the temporal sequencing of multiple movements without sensory guidance (Tanji and Shima 1994) or in the poor ability of SMA-lesioned monkeys to select appropriate movements when no sensory cue is available (Thaler et al. 1995; Chen et al. 1995).

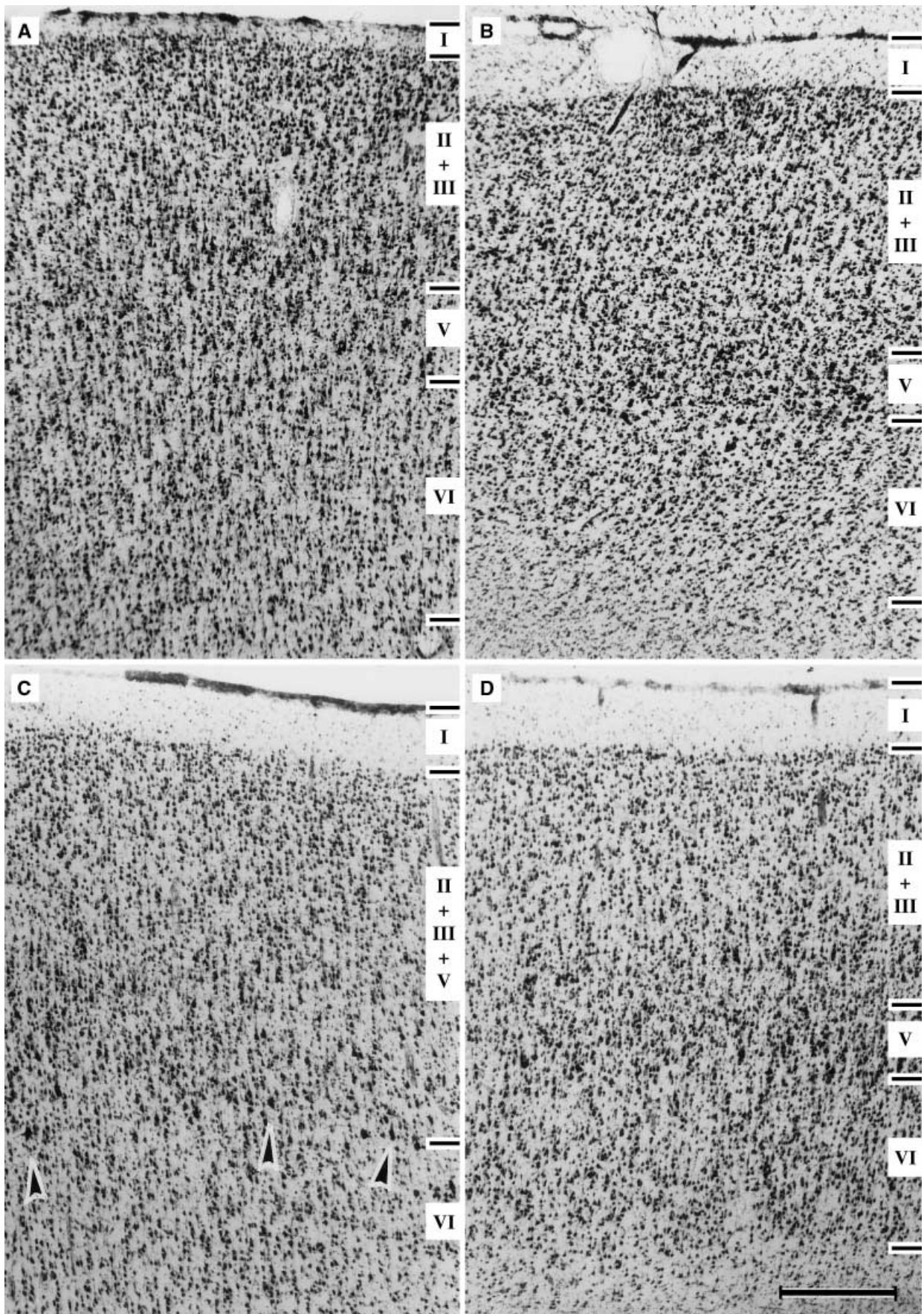
Proximal versus distal limb movements The old notion that the SMA is mainly involved in proximal movements has mainly originated from ICMS studies (see above) which found that proximal movements are much more represented than are distal movements. Unit recording studies, however, have detected neuronal activity in the SMA associated both with proximal and distal movements

(Brinkman and Porter 1979; Tanji and Kurata 1979). Even when the movements were specifically limited to those of the hand, neuronal activity has been observed in the SMA (Okano and Tanji 1987; Thaler et al. 1988; Tanji et al. 1988). How can this conflict between ICMS and unit recording data be resolved? Tract tracing studies have yielded conflicting results. Luppino et al. (1993) injected tracers into the arm field of the SMA and found retrogradely labeled neurons in area F1 almost exclusively on the free cortical surface (representation of the proximal arm; see above), whereas Tokuno and Tanji (1993) found that the F1 representations of the proximal arm (on the cortical convexity) and the fingers (in the rostral bank of the central sulcus) are connected with the SMA. In a recent review article (1994), Tanji has pointed out that ICMS may yield misleading results in non-primary motor areas. When motor effects are to be evoked from secondary motor areas, higher electrical currents or longer trains of stimuli are needed. When using such parameters, motor effects are often elicited in multiple muscles, giving rise to complex multijoint movements and masking motor effects in smaller distal muscles. In addition, the stimuli induced by ICMS are rather artificial in nature and this should caution against an overinterpretation of the outcome of high-frequency multiple-pulse electrical stimulation with respect to the physiological organization of a non-primary motor area (Tanji 1994). Hence, the SMA seems to be involved in proximal and distal movements and the old concept should be discarded.

Motor preparation Tanji et al. (1980) instructed monkeys to push or pull a handle depending on a forthcoming trigger signal. During the preparatory period, the neuronal activity in the SMA increased or decreased depending on whether the monkey was intending to push or pull the handle. The preparation for different movements was reflected by differential neuronal activity. These findings could be replicated in subsequent studies (Kurata and Wise 1988; Alexander and Crutcher 1990). However, preparatory activity for movements in different directions is found in many other cortical areas, including area F1, the lateral premotor cortex, prefrontal cortex, parietal cortex, and basal ganglia (see Tanji 1994 for references). One may wonder, whether there are any paradigms that describe more specifically the role that the SMA plays in the preparation for forthcoming movements. This seems to be the case for a motor preparation that implies a greater degree of complexity. Differential activity was found in the SMA when an additional instruction signal was introduced that instructed the monkey what to do when the trigger signal came up (i.e., instruction signal A → press a key in response to trigger signal X, but withhold the movement in response to Y; instruction signal B → do just the opposite; Tanji and Kurata 1985), when the animal prepared to move a single hand or both hands (Tanji et al. 1988), or when the monkey prepared to make sequential movements under sensory guidance or based on memory (Mushiaki et al. 1991).

Bimanual coordination Brinkman (1981, 1984) evaluated the influence of a unilateral SMA lesion on bimanual hand coordination in monkeys. Monkeys had to retrieve a food pellet lodged in a hole in a perspex sheet. A normal animal pushed from above with the index finger of the preferred hand, while the non-preferred hand was cupped under the hole, anticipating the catch of the falling pellet. A monkey with a unilateral SMA lesion (opposite the non-preferred hand) used both hands in a mirror-like way, pushing the food from above with one hand and from below with the other hand. The findings were interpreted that in a lesioned animal the intact SMA would influence the motor outflow from both sides, whereas in a normal animal the SMA on one side would inform the opposite side of intended or ongoing movements in one side. Tanji et al. (1987, 1988) trained monkeys to press a key with the right, left or both hands simultaneously depending on which instruction signal was given prior to a trigger signal. Neuronal activity in the SMA changed in relation to the movement of only one hand (right or left) or both hands together. Taken together, the findings suggest that the SMA is involved in a process of transformation of information about the intended usage of both hands into the pattern of neural activity for movement execution (Tanji 1994).

Differences in function between areas F3 (SMA proper) and F6 (pre-SMA) In recent years the subdivision of the “classical” SMA into a caudal (SMA proper or area F3) and a rostral (pre-SMA or area F6) region has gained wide acceptance in the neuroscience community. For this reason, there is now an increasing number of studies available that try to elucidate the functional differences between the two areas. Single unit recording studies have shown that neurons responding to visual stimuli are found mainly in the pre-SMA (Matsuzaka et al. 1992), whereas neurons in the SMA proper respond mainly to somatosensory stimuli (Hummelsheim et al. 1988; Matsuzaka et al. 1992). When performing a motor task, set-related neuronal activity long before the onset of a movement is present almost exclusively in the pre-SMA (Rizzolatti et al. 1990; Alexander and Crutcher 1990; Matsuzaka et al. 1992), whereas phasic activity, more frequently time locked to the movement onset is more common in the SMA proper (Alexander and Crutcher 1990; Matsuzaka et al. 1992). In addition, pre-SMA neurons show more complex firing patterns related to arm movements. Their activity is influenced by the distance of the objects from the monkey, and frequently the neuronal activity depends on whether the animal can or cannot reach and grasp the object that is presented (Rizzolatti et al. 1990). In two very recent studies monkeys were trained to perform three different movements sequentially in a temporal order. Neuronal activity was found mainly in the pre-SMA (but only infrequently in the SMA proper and not at all in the primary motor cortex) when the animals were required to discard a current motor plan and develop a new plan appropriate for the next movement (Shima et al. 1996; Matsuzaka



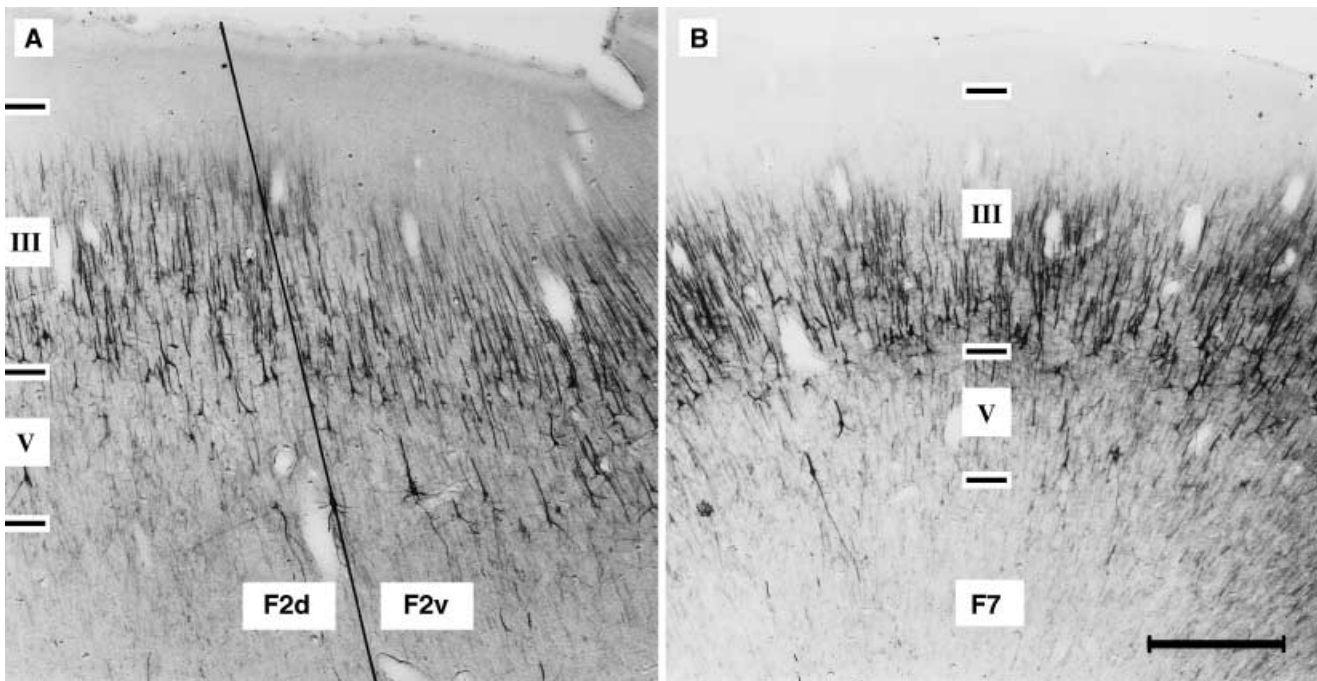


Fig. 7 SMI-32 immunohistochemistry of the border between areas F2d and F2v (**A**) and area F7 (**B**). Pyramidal cells in layers III and V are immunopositive. Emerging small immunoreactive pyramids in layer V mark the border between areas F2d and F2v. In area F7, the cell bodies of layer III pyramids are slightly larger. *Roman numerals* indicate cortical layers. *Bar* 500 μ m (**A,B**)

Dorsolateral premotor cortex (PMd; areas F2 and F7)

Microstructure

Similar to areas F3 and F6 on the mesial cortical surface, different investigators have proposed various maps of the PMd which are also plagued by the subjective nature of microstructural parcellation. Most authors have subdivided the PMd into two areas, a caudal one and a rostral one. The position of the border between the two areas, however, is highly variable. It was set at a level just rostral to the genu of the arcuate sulcus by Vogt and Vogt (1919), further rostrally (towards the prefrontal cortex) by von Bonin and Bailey (1947), or further caudally (towards the primary motor cortex) by Barbas and Pandya (1987).

In contrast to these maps, the parcellation of the PMd into a caudal area F2 and a rostral area F7 is supported by converging results from histochemical (Matelli et al. 1985), cytoarchitectonic (Matelli et al. 1991), receptor autoradiographic (Geyer et al. 1998a), and most recently immunohistochemical data on the distribution of neurofilament proteins with the monoclonal antibody SMI-32 (Fig. 7; Geyer et al. 1998b; Gabernet et al. 1999; Geyer et al. 2000; Petrides et al. 2000). In a Nissl-stained section, area F2 is poorly laminated like areas F1 and F3 (Fig. 6A). Similar to area F3, scattered giant pyramidal cells are present only in its caudal part towards the border to area F1. A narrow band of medium-sized pyramids can be found at the border between layers III and V. The cell density in layers III and V is slightly lower than in area F3. Area F7 is clearly laminated and layer V is prominent (like in area F6; Fig. 6B). The cell density in area F7 is comparable to area F6 but the pyramidal cells are somewhat smaller. Despite these obvious interareal differences in cytoarchitecture, the borders

and Tanji 1996). These findings are in line with the massive input which the pre-SMA (but not the SMA proper) receives from the prefrontal cortex (see above). This prompted Rizzolatti et al. (1998) to argue that the pre-SMA represents a “supramotor” control center that triggers a movement only when external contingencies (close or distant stimulus, presence or absence of an obstacle, physical possibility to act) and motivational factors allow it.

In summary, the SMA is involved in many different aspects of planning and executing voluntary movements and it would be too simplistic to attribute its “function” to one or a few “categories” of cortical motor control. Studies in non-human primates suggest that the pre-SMA (or area F6) seems to be more involved than the SMA proper (or area F3) in planning or acquiring a spatiotemporal pattern of movements when a subject needs to accomplish a motor task incorporating a novel requirement imposed by changes in the environmental conditions (Tanji 1996).

◀ **Fig. 6** Cytoarchitecture of areas F2 (**A**), F7 (**B**), F4 (**C**), and F5 (**D**). As on the mesial surface, the cellular density in layers III and V increases and the cortical layers stand out more clearly in a caudo-rostral direction (from areas F2 and F4 to areas F7 and F5). *Arrowheads* mark large layer V pyramidal cells scattered throughout the caudal and dorsomedial part of area F4. *Roman numerals* indicate cortical layers. *Bar* 500 μ m (**A–D**). **A,B** reprinted from Geyer et al. (1998a) with permission from John Wiley & Sons

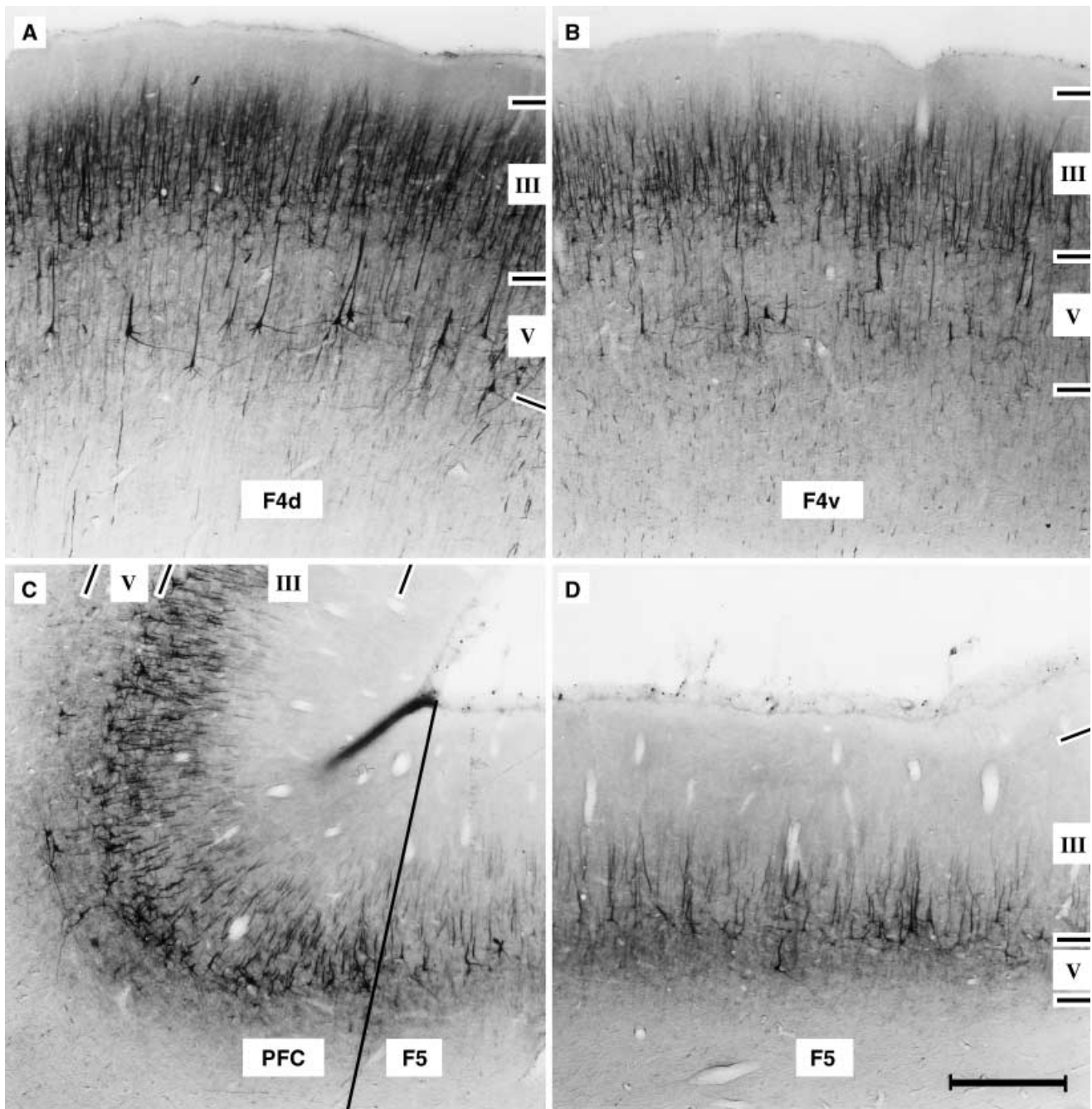


Fig. 8 SMI-32 immunoarchitecture of areas F4d (A), F4v (B), the border between area F5 and the prefrontal cortex (PFC; C), and area F5 (D). Pyramidal cells in layers III and V are immunopositive. Differences in layer V immunoreactive pyramids define a dorsal (area F4d) and a ventral (area F4v) region within area F4. Immunoreactivity in area F5 is very weak; a sharp increase marks the border between area F5 and the PFC. Roman numerals indicate cortical layers. Bar 500 μ m (A–D)

between the two areas are very difficult to define in Nissl-stained material, since at a border the cytoarchitectonic features tend to merge gradually and not to change abruptly in a step-like fashion. The advent of a new technique, the immunostaining of neurofilaments with the antibody SMI-32, has greatly facilitated a more

precise and reliable definition of interareal borders. With SMI-32 immunohistochemistry, differences in size, shape, and packing density of immunopositive layer III and V pyramidal cells define the borders of areas F2 and F7 more clearly than do differences in cytoarchitecture (Geyer et al. 1998b; Geyer et al. 2000). Spur and superior arcuate sulcus separate areas F2 and F7 from the PMv and the prefrontal cortex (Fig. 1C). Area F2 extends from 2 to 3 mm laterally from the midline to the fundus of the arcuate spur and the fundus of the caudal part of the superior arcuate sulcus. The border between areas F2 and F7 lies slightly anterior to the genu of the arcuate sulcus. Area F7 occupies the rostral part of the PMd from 2 to 3 mm laterally from the midline to the fundus

of the rostral part of the superior arcuate sulcus. Recent evidence from SMI-32 immunohistochemistry indicates that the fine-grained functional organization within area F2 (see below) may also be reflected on a structural level: differences in layer V immunoreactive neurons define a dorsal (area F2d) and a ventral (area F2v) region (Fig. 7A). The border between areas F2d and F2v lies at the level of the superior precentral dimple and cannot be detected cytoarchitectonically in Nissl-stained material (Geyer et al. 1998b; Geyer et al. 2000).

Connectivity

The thalamic input to area F2 originates from the nucleus ventralis posterolateralis pars oralis (VPLo), nucleus ventralis lateralis pars caudalis (VLc), and nucleus ventralis lateralis pars oralis (VLo). The dorsal part of area F7 (supplementary eye field (SEF), see below) receives its thalamic input mainly from area X of Olszewski (1952), nucleus ventralis anterior pars parvocellularis (VApc) and magnocellularis (VAmc). Ventral area F7 is connected with the VApc, area X, the VLc, and the VPLo (Matelli and Luppino 1996). Similar to areas F3 and F6, area F2 as well as dorsal and ventral area F7 are also elements of different subcortical motor loops. Areas F3 and F2 seem to belong to the same loop, being the target (via the nucleus VLo) of the putamen and pallidum, whereas areas F6 and ventral area F7 belong to another loop, receiving their input (via the nucleus VApc) from the caudate nucleus. Dorsal area F7 (the SEF) is part of a subcortical "oculomotor circuit" (Matelli and Luppino 1996).

Area F2 is connected with area F1, but not with the prefrontal cortex. Conversely, area F7 is strongly connected with the prefrontal cortex but there are no direct connections with area F1 (Barbas and Pandya 1987; Luppino et al. 1990). Areas F2 and F7 receive rich cortical input from the posterior parietal cortex. These connections are the anatomical basis of several parieto-frontal circuits that are (as described above) important functional units of the cortical motor system (Rizzolatti et al. 1997; Matelli et al. 1998; Rizzolatti et al. 1998). The region of area F2 around the superior precentral dimple receives its "predominant" parietal input from area PEip in the medial bank of the intraparietal sulcus and from area PEc in the caudal part of the superior parietal lobule ("*PEip/PEc – F2 dimple*" circuit; Figs. 1B,C, 2A). The medial intraparietal (MIP) area in the medial bank of the intraparietal sulcus and area V6A in the parieto-occipital sulcus are connected with the ventrorostral part of area F2 ("*MIP/V6A – F2 ventrorostral*" circuit; Figs. 1B, 2A). Area PGm on the mesial surface of the superior parietal lobule projects predominantly to ventral area F7 ("*PGm – F7 ventral*" circuit; Figs. 1A, 2A). Dorsal area F7 (the SEF) is the target of the lateral intraparietal (LIP) area in the lateral bank of the intraparietal sulcus ("*LIP – F7 dorsal*" circuit; Fig. 1B; Huerta and Kaas 1990).

Area F2 sends descending projections to the spinal cord. Area F7 projects to the superior colliculus (mainly from dorsal area F7 (the SEF)) and to the reticular formation in the brain stem (Fries 1985; Keizer and Kuypers 1989; He et al. 1993).

Function

Since the circuits connecting the parietal cortex with areas F2 and F7 are not only anatomical but also functional entities, the discussion of the functional aspects of areas F2 and F7 will be based on a more detailed description of the functional properties of these parieto-frontal loops.

"PEip/PEc – F2 dimple" and "MIP/V6A – F2 ventrorostral" circuit Neurons recorded from the part of area PE lying in the medial bank of the intraparietal sulcus (area PEip = the rostral part of area PEa of Pandya and Seltzer (1982) = that part of area PEa that gives rise to cortico-spinal projections (Matelli et al. 1998)) respond to somatosensory stimuli (Mountcastle et al. 1975; Iwamura and Tanaka 1996) often in association with arm movements (Kalaska et al. 1990). Neurons in the caudal part of the superior parietal lobule (area PEc) and the rostrally adjoining area PE (with which area PEc is richly connected; Pandya and Seltzer 1982) are also involved in the processing of somatosensory stimuli for movement organization (Colby and Duhamel 1991; Galletti et al. 1996). It seems that areas PEip and PEc are mainly involved in somatosensory aspects of cortical motor control.

The situation is different in area MIP (Colby et al. 1988) in the medial bank of the intraparietal sulcus (caudal to area PEip) and in area V6A (Galletti et al. 1996) in the parieto-occipital sulcus. Neurons in area MIP respond to somatosensory and visual stimuli (Colby and Duhamel 1991), whereas neurons in area V6A respond to visual stimuli but also in association with eye or arm movements (Galletti et al. 1996; Galletti et al. 1997). In contrast to areas PEip and PEc, areas MIP and V6A seem to be involved in somatosensory and visual aspects of motor control.

Areas PEip and PEc (mainly somatosensory information) project to the region of area F2 around the superior precentral dimple, areas MIP and V6A (somatosensory and visual information) to the ventrorostral part of area F2.

Area F2 is electrically excitable and has a rough somatotopic organization. Leg movements are represented dorsal to and arm movements ventral to the superior precentral dimple (Fig. 1C). Proximal and distal movements are poorly separated (Kurata 1989; Dum and Strick 1991; He et al. 1993; Godschalk et al. 1995). Unit recording studies confirm the differential projections of the two parieto-F2 circuits. Responses to sensory stimuli can be found throughout area F2. However, visually driven neurons are mainly concentrated in the ventrorostral sector of area F2 (Fogassi et al. 1999). By introducing a delay period between the instruction signal and the movement

trigger signal, area F2 neurons can be grouped into three different classes: (1) neurons exhibiting a visually driven phasic response immediately after the instruction signal (signal-related neurons), (2) neurons showing sustained activity during the delay period between the instruction and the trigger signal (set-related neurons), and (3) neurons firing between the trigger signal and the movement onset (movement-related neurons). These three classes of neurons are distributed along a gradient within area F2, i.e., signal-related neurons are predominant in the rostral part of area F2 (towards area F7), set-related neurons in the central part, and movement-related neurons in the caudal part (towards area F1; Tanne et al. 1995; Johnson et al. 1996; Caminiti et al. 1996).

In conclusion, the “PEip/PEc – F2 dimple” circuit appears to be involved in planning and controlling arm (and leg) movements on the basis of somatosensory information. In contrast, the “MIP/V6A – F2 ventrorostral” circuit uses somatosensory and visual information, probably for the same purpose. Monitoring and controlling arm position during the transport phase of the hand towards the target could be one of the major functions of this circuit (Rizzolatti et al. 1998).

“PGm – F7 ventral” circuit Neurons in area PGM (Pandya and Seltzer 1982) on the mesial surface of the superior parietal lobule fire during arm and/or eye movements (Ferraina et al. 1997a,b).

Area PGM projects predominantly to the ventral part of area F7. Neurons in area F7 respond to arm movements or to visual stimuli. In contrast to area F2, visually responsive neurons in area F7 are more numerous and they do not need a subsequent movement in order to become active (di Pellegrino and Wise 1991). When tested in a paradigm in which reaching movements were (1) triggered by and directed toward the same visual (or acoustical) target or (2) triggered by a sensory cue but directed towards a different spatial target, some area F7 neurons responded only in the first condition (Vaadia et al. 1986). Lesion studies suggest a crucial involvement of area F7 (and possibly rostral area F2 as well) in stimulus-response associations. Monkeys were trained to perform a conditional association task, e.g., to make arbitrary goal-directed movements in response to colored stimuli. After the lesion, no obvious motor deficit was present but the animals were no longer able to perform the task (Halsband and Passingham 1982; Petrides 1982).

In conclusion, the “PGm – F7 ventral” circuit appears to be important for conditional movement selection and for the visual localization of stimuli in space as a prerequisite for reaching movements.

“LIP – F7 dorsal” circuit Neurons in area LIP (Andersen et al. 1985; Blatt et al. 1990) in the lateral bank of the intraparietal sulcus encode visual signals (Robinson et al. 1978) that are related to memory (Gnadt and Andersen 1988) and to saccades (rapid eye movements) towards the target (Goldberg et al. 1990; Barash et al. 1991). Neurological activity can be modulated by attention (Bushnell et al.

1981) and by the position of the eye in the orbit (Andersen et al. 1990). More recent studies have shown that area LIP contributes to a stable internal representation of space by dynamic updating or remapping visual information in combination with eye movements (Duhamel et al. 1992; Colby et al. 1995). This may be a neural basis of the everyday experience that despite the fact that we constantly move our eyes (and thus activate different retinal neurons) we perceive a stable visual world.

Area LIP projects to the dorsal part of area F7 that contains the SEF. In contrast to area F2, F7 is electrically scarcely excitable (Godschalk et al. 1995). An exception is the SEF from which converging or goal-directed saccades can be evoked (Schlag and Schlag-Rey 1987). Neurons in the SEF (and in the frontal eye field (FEF)) fire before a saccade is initiated (Hanes et al. 1995). However, neuronal activity in the SEF is higher than in the FEF when monkeys learn new associations between visual cues and the direction of saccades (Chen and Wise 1995). The SEF seems to be more involved than the FEF in learning-related processes. An interesting new concept has recently been introduced by Olson and Gettner (1995, 1996). Monkeys were trained to perform saccades to the right or left end of a horizontal bar that was presented at various locations on a video screen. A SEF neuron would fire strongly when the saccade was directed to the left end of the bar (but much weaker when directed to the right end) irrespective of the location of the bar on the screen. About half of the SEF neurons showed object-related direction selectivity, each neuron favoring a particular location on the object, e.g., top, left end, bottom, right end, or center. In other words, SEF neurons encode the direction of an impending saccade relative to an object-centered frame of reference.

The “LIP – F7 dorsal” circuit may be important for controlling saccades that are made during head or body movements or, more general, saccades concerned with complex motor programming (Pierrot-Deseilligny et al. 1995).

Ventrolateral premotor cortex (PMv; areas F4 and F5)

Microstructure

The maps of the PMv proposed by different investigators are even more variable than those of the PMd. Not only do they differ in terms of location and size of the areas but also in their number: two regions were defined by von Bonin and Bailey (1947; areas FBA and FCBm) and Barbas and Pandya (1987; areas 6Va and 6Vb) whereas Vogt and Vogt (1919) proposed three areas: 6a α , 6b α , and 6b β . Yet another area, namely a rostral extension of the primary motor cortex was introduced by Vogt and Vogt (1919; area 4c) and Barbas and Pandya (1987; area 4C). In both maps, this latter area is bordered medially by the arcuate spur and rostrally by the inferior arcuate sulcus.

Seen against this background, a multimodal approach based on different but complementary techniques yields more reliable and also (from a functional point of view; see below) more valid data. Based on a histochemical and cytoarchitectonic analysis, two areas have been proposed by Matelli et al. (1985): area F4 caudally and area F5 rostrally. More recently, receptor autoradiographic data (Matelli et al. 1996) and immunohistochemical data on the distribution of neurofilament proteins with the antibody SMI-32 (Fig. 8; Matelli et al. 1996; Geyer et al. 1998b; Petrides et al. 2000) have confirmed this map. In Nissl-stained material, area F4 is poorly laminated (like areas F1, F2, and F3; Fig. 6C). Similar to area F2, pyramids increase in size from superficial to deep layer III but in area F4 the overall cell density is lower. Scattered very large pyramidal cells (arrowheads in Fig. 6C) are present in its caudal (towards area F1) and especially dorsomedial part (towards the arcuate spur). Area F5 is clearly laminated with a prominent layer V (Fig. 6D). The cell density in area F5 is higher than in F4. Spur and inferior arcuate sulcus separate areas F4 and F5 from the PMd and the prefrontal cortex (Fig. 1C). Area F4 lies rostral to area F1, extending dorsomedially to the arcuate spur and ventrolaterally to the rostralmost extension of the primary somatosensory cortex at the level of the inferior precentral dimple. Area F5 occupies the rostral part of the PMv and abuts on the prefrontal cortex in the fundus of the inferior arcuate sulcus. Preliminary evidence from SMI-32 immunohistochemistry indicates that (similar to areas F2d and F2v within area F2) a more fine-grained structural organization is evident also within area F4: differences in layer V immunoreactive neurons define a dorsal (area F4d; Fig. 8A) and a ventral (area F4v; Fig. 8B) region within area F4 (Geyer et al. 1998b).

Connectivity

Area F4 receives a large thalamic projection from the nucleus ventralis lateralis pars oralis (VLo) and additional projections from area X of Olszewski (1952), nucleus ventralis posterolateralis pars oralis (VPLo), and nucleus ventralis lateralis pars caudalis (VLc). Area F5 receives its main thalamic input from area X. Additional projections to area F5 arise from the nucleus VPLo and VLc. Similar to areas F2, F3, F6, and F7, areas F4 and F5 are also elements of different subcortical motor loops. Area F4 is the target (via the nucleus VLo) of the putamen and pallidum, whereas area F5 receives its input (via area X) from the cerebellum (Matelli et al. 1989).

On a cortical level, area F5 (but not F4) receives afferents from the prefrontal cortex in the lateral bank of the principal sulcus. Area F4 is connected more strongly with area F3 (SMA proper) than with area F6 (pre-SMA). Conversely, area F5 is connected more strongly with area F6 than with F3. Area F1 receives input from the entire area F4 but only from a small part of area F5 in the caudal bank of the inferior arcuate sulcus (Matelli et al. 1986; Luppino et al. 1993). Similar to areas F2 and

F7, areas F4 and F5 also receive rich cortical input from the posterior parietal cortex. These connections also form several parieto-frontal circuits that are important functional units for the cortical control of reaching and grasping (Rizzolatti et al. 1997; Rizzolatti et al. 1998; Luppino et al. 1999). Area F4 receives its “predominant” parietal input from the ventral intraparietal (VIP) area in the fundus of the intraparietal sulcus (“VIP – F4” circuit; Figs. 1B, 2B). The anterior intraparietal (AIP) area in the lateral bank of the intraparietal sulcus projects mainly to the part of area F5 in the caudal bank of the inferior arcuate sulcus (“AIP – F5 bank” circuit; Figs. 1B, 2B), whereas area PF in the inferior parietal lobule projects predominantly to the sector of area F5 on the cortical convexity (“PF – F5 convexity” circuit; Figs. 1C, 2C).

Area F4 sends descending projections to the brain stem and spinal cord. The dorsal part of area F4 (arm representation; see below) projects to the brain stem reticular formation and the cervical spinal cord, the ventral part (face representation; see below) to the brain stem nuclei that control the orofacial muscles. Area F5 projects almost exclusively to the reticular formation except for a small sector in the caudal bank of the inferior arcuate sulcus that is also connected with the spinal cord (Keizer and Kuypers 1989; Dum and Strick 1991; He et al. 1993).

Function

The discussion of the function of areas F4 and F5 will also follow a more detailed description of the properties of these parieto-F4 and parieto-F5 loops.

“VIP – F4” circuit In contrast to the eye-centered representation of space found in area LIP, neurons in area VIP (Colby et al. 1993) in the fundus of the intraparietal sulcus code space with respect to a head-centered frame of reference. Neurons in area VIP are typically bimodal (visual and somatosensory), i.e., they respond to a visual stimulus moving in the space within reaching distance around the body (peripersonal space; Colby et al. 1993) but also to light touch on the skin (Duhamel et al. 1991). The somatosensory receptive fields of these bimodal neurons are typically found on the head and face. Most interestingly, the visual and somatosensory fields of an individual VIP neuron match in location (a neuron that responds, e.g., to a visual stimulus in the upper right visual field also responds to touch in the upper right part of the face), size (a neuron with, e.g., a large visual receptive field also has a large somatosensory receptive field), and preferred direction (a neuron that responds, e.g., to a visual stimulus moving from left to right also responds to a somatosensory stimulus moving in the same direction across the skin). This congruence is maintained when the eyes move or, in other words, the visual receptive field of a given VIP neuron remains anchored to its somatosensory counterpart even when the stimulus activates a different set of retinal neurons. Thus,

space is coded relative to a head-centered (and not eye-centered) frame of reference.

Area VIP projects predominantly to area F4. Area F4 is electrically excitable and organized in a somatotopic fashion: arm movements are represented dorsally and oro-facial movements ventrally (Fig. 1C). ICMS shows that, in contrast to area F1, thresholds for eliciting movements are higher in area F4, evoked movements are more complex (involving more than two articulations or involving noncontiguous articulations or body parts, e.g., shoulder and wrist), and mainly proximal movements can be elicited from the arm field of area F4 (Kurata and Tanji 1986; Gentilucci et al. 1988, 1989; Hepp-Reymond et al. 1994). Similar to area VIP, many neurons in area F4 are also bimodal, with somatosensory receptive fields on the face, neck, trunk or arms and visual receptive fields in the peripersonal space and in register with their somatosensory counterparts. Approaching objects are the most effective visual stimuli, whereby an increase in stimulus velocity typically expands the depth of the receptive field. In most cases, the visual receptive field does not move when the monkey moves the eyes. However, it does move when the monkey changes the position of the body part to which it is anchored. Hence, in area F4, space is also coded in body-parts-centered coordinates (Gentilucci et al. 1988; Graziano et al. 1994; Fogassi et al. 1996). Many F4 neurons fire upon reaching movements, i.e., movements of the proximal arm but not upon movements of the distal arm. Often a correlation is found between the positions of the somatosensory and visual receptive fields and the direction of the effective movement (a neuron with, e.g., a tactile and visual receptive field in the face region also fires during a movement towards the space above the shoulder; Gentilucci et al. 1988).

These findings prompted Rizzolatti and colleagues (1998) to conclude that the "VIP – F4" circuit plays a role in encoding the peripersonal space and in transforming object locations into appropriate movements toward them.

"AIP – F5 bank" circuit Neural activity in area AIP (Sakata et al. 1995) in the lateral bank of the intraparietal sulcus was studied in monkeys trained to grasp different objects that required different patterns of hand and finger movements (pull lever with four fingers, push button with thumb, pull knob in a groove with tip of thumb and index finger, pull protruding knob with side grip of thumb and index finger) or simply to fixate these objects. The tasks were performed in light and darkness. Three different types of neurons can be differentiated in area AIP. Motor-dominant neurons are active during object manipulation in light and darkness but not during object fixation. Most of them are more or less selective for one object. Visual-and-motor neurons have visual and motor properties. They are more active during object manipulation in light than in darkness or during object fixation. Visual-dominant neurons have purely visual properties. They respond to object manipulation

in light and to object fixation but remain silent during object manipulation in darkness. An interesting finding is that the activity of neurons with motor properties is not influenced by the position of the object in space, which shows that these neurons encode hand and finger but not proximal arm movements. Furthermore, neurons with motor and visual properties prefer the same object for fixation and manipulation, suggesting that these neurons match the intrinsic geometric properties of the object with the appropriate hand movement for grasping it. In a delayed-manipulation task, this information is even maintained for a short period after the object has disappeared (Taira et al. 1990; Sakata et al. 1995; Murata et al. 1996). When area AIP is reversibly inactivated by microinjecting muscimol, no major deficits in reaching are obvious, but the monkey is no longer able to appropriately preshape its hand and fingers in order to accommodate the object (Gallese et al. 1994). The results suggest that area AIP is crucially involved in the visual guidance of goal-directed hand movements.

Area AIP projects mainly to the part of area F5 in the caudal bank of the inferior arcuate sulcus. Area F5 is electrically much less excitable than area F4. Movements can be elicited almost exclusively from the sector of area F5 lying in the caudal bank of the inferior arcuate sulcus. Area F5 is organized somatotopically. Similar to area F4, arm movements are represented dorsally and oro-facial movements ventrally (Fig. 1C). In contrast to area F4, the distal arm is mainly represented in area F5 (whereas the proximal arm in area F4; Kurata and Tanji 1986; Gentilucci et al. 1988, 1989; Hepp-Reymond et al. 1994). Most area F5 neurons discharge not upon individual movements made by the animal but upon specific goal-directed motor acts, typically when grasping an object with a precision grip (i.e., opposition of the thumb and index finger), finger prehension (i.e., opposition of the thumb to the other fingers), or whole hand prehension (i.e., flexion of all fingers around the object). When objects with different geometric properties are grasped in a similar way, similar neuronal responses are obtained. A fraction of these neurons also responds to somatosensory stimuli with a good correlation between the neuron's preferred type of grip and the location of the receptive field (e.g., a precision grip neuron has its somatosensory receptive field on the thumb and index finger). Some neurons also respond to visual stimuli, again with a good correlation between the neuron's preferred type of grip and the geometry of the object the cell is responding to (e.g., a precision grip neuron is also activated by a small visual stimulus but not by a large one; Rizzolatti et al. 1988). Even when a motor response to the object is not required, many F5 neurons discharge to its mere visual presentation (Murata et al. 1997). The motor deficits following reversible inactivation of area F5 are very similar to the symptoms upon inactivation of area AIP (see above): severe disturbance of hand preshaping and object grip, but no paralysis and no deficit in reaching (Gallese et al. 1997).

In sum, the “AIP – F5 bank” circuit is important for coding the object’s intrinsic geometric properties and transforming them into appropriate goal-directed hand movements (Jeannerod et al. 1995). Or, to put it differently, each time an object is observed, its visual features are automatically (no matter whether a movement is intended or not) “translated” into a “vocabulary” of motor acts stored in area F5.

“PF – F5 convexity” circuit Neurons located in the part of area F5 lying on the cortical convexity have the same motor properties as cells in the “F5 bank” region, i.e., they also discharge upon specific goal-directed motor actions. Only in the “F5 convexity” sector, however, can a group of neurons be found that are endowed with very intriguing visual properties such as can be seen in the following paradigm. The monkey observes the experimenter grasping a small piece of food placed on a tray. The tray is then moved towards the monkey and the monkey itself grasps the food morsel. The neurons discharge when the experimenter grasps the food, stop firing when the food is moved towards the monkey, and discharge again when the monkey grasps the food. In other words, these neurons fire both when the animal performs a goal-directed motor action and when the animal observes another individual performing an action similar to that encoded by the neuron. Because of this correspondence between performing and observing an action, these neurons were termed “mirror neurons” (Gallese et al. 1996; Rizzolatti et al. 1996b). Mirror neurons, in order to be visually triggered, require an interaction between the agent of the action and the object. Observing the agent alone or the object alone (i.e., without interaction) is ineffective. The degree of correspondence between performing and observing an action can be very high. A typical mirror neuron fires when the monkey grasps an object and when the animal observes another individual grasping the same object. However, when the object is grasped with a tool (e.g., a forceps or a pair of pliers) instead of the hand, the neuron does not respond. On the other hand, the neuron does fire when the animal grasps the object in darkness. This indicates that the neuron indeed encodes a motor program and is not triggered by visual feedback.

How can this correspondence between acting and observing be explained? A straightforward interpretation would be that mirror neurons are related to motor preparation. A monkey that observes another monkey grasping food in a natural setting might implicitly prepare a similar action, e.g., in order to beat potential competitors for food. This explanation, however, is inappropriate since the neural activity decreases towards the end of observing the object and does not increase again until the monkey itself grasps the object. Were the activity indeed related to motor preparation, it should increase rather than decrease towards the end of the observation phase. A different interpretation is that mirror neurons are involved in the “understanding” of motor events (i.e., the ability to recognize that an individual is performing an

action, to differentiate this action from others analogous to it, and to use this information in order to act appropriately; di Pellegrino et al. 1992). When an animal performs a specific motor act in a natural environment (e.g., grasping food), it knows from experience the consequences (in this case the feeling of being satiated). The motor action and its implicit meaning are encoded in a specific neuronal discharge pattern. Mirror neurons match this action (and its meaning) with the observation of the same action (and its meaning) in another individual. Performing an action (with its implicit meaning) and observing the same action result in the same neuronal discharge pattern. Hence, it may be assumed that observing an action in another individual also entails extracting (and thus “understanding”) its biological meaning.

The “F5 convexity” region receives its main parietal input from area PF (Pandya and Seltzer 1982) in the rostral inferior parietal lobule. Preliminary observations have revealed that a similar observation/execution matching system also exists in area PF (Fogassi et al. 1998).

Taken together, the “PF – F5 convexity” circuit is a system that matches observation with execution of a motor action. This suggests an important cognitive role for these parts of the inferior parietal and lateral premotor cortex, namely internally representing and thus “understanding” motor events.

The isocortical motor system in humans

The data on the motor system in macaques that have been described above are based on a very elementary biological principle: what differs in structure (in this context: microstructure of the cerebral cortex) should also differ in function. In other words, neurons with similar electrophysiological properties should lie within the same cortical area and, conversely, the properties of neurons should change across a microstructural border. This tenet can be tested in a straightforward and *direct* way in macaques, since upon completion of the electrophysiological experiments the brain can be sectioned, sections can be cell-stained, and penetration sites can be *directly* correlated with the microstructural (e.g., cytoarchitectonic) pattern. This match of cytoarchitecture with function has been demonstrated many times in macaques and has led to the very elaborate view of the isocortical motor system in this primate species.

Not so in humans. For obvious ethical reasons, functional *in vivo* and anatomical post mortem studies cannot be performed in the same brain. This precludes a *direct* correlation of microstructure and function. As a consequence, investigators have sought *indirect* ways to achieve a match between structure and function.

One way is to start from anatomy. Several microstructural maps of the human frontal cortex have been published so far (Campbell 1905; Smith 1907; Brodmann 1909; Vogt and Vogt 1919; von Economo and Koskinas 1925; Bailey and von Bonin 1951; Sarkissov et

al. 1955; Braak 1980). Especially Brodmann's (1909) map has been of tremendous impact over the last decades (and is still found in many neuroscience and neurology textbooks). However, these "classical" maps were published in print format. This puts them at a clear disadvantage when structural data from these maps are to be matched with functional data obtained from different brains. First, these maps are schematic drawings that reflect the topographical situation in one representative brain and do not address the problem of interindividual macro- (see, e.g., Ono et al. 1990) and microanatomical (see, e.g., Rademacher et al. 1993) variability. Second, these maps are "rigid" and are not based on a spatial reference system. They cannot be adapted to an individual brain and multimodal integration of structural and functional data is impossible. More recently published atlases, e.g., the reference system of Talairach and Tournoux (1988), are of limited value as well, as their cortical maps are not based on genuine microstructural data (the authors seem to have transferred each area from Brodmann's schematic drawing to a corresponding position on the cortex of their reference brain). In addition, Talairach and Tournoux give only the approximate position of an area (borders between areas are not indicated) nor do they address the problem of interindividual variability.

A complementary approach is to start from a functional point of view. Over the last years, noninvasive imaging techniques (e.g., positron emission tomography (PET) and, more recently, functional magnetic resonance imaging (fMRI)) have mapped the cerebral cortex with ever-increasing spatial resolution, but they relate foci of activation only to macroanatomical landmarks (i.e., gyri and sulci). Plenty of evidence in macaques and other non-human primates, however, has shown that it is microstructure that parallels function. Unfortunately, most microstructurally defined interareal borders in the human cortex do not match macroanatomical landmarks and they are topographically quite variable across different individuals (Rademacher et al. 1993; Roland and Zilles 1994; Rajkowska and Goldman-Rakic 1995; Geyer et al. 1996; Roland and Zilles 1996; White et al. 1997; Roland et al. 1997; Geyer et al. 1999; Amunts et al. 1999, 2000). Hence, structural-functional correlations based only on macroanatomy are questionable and may account for at least some of the conflicting results functional imaging studies have provided in recent years, e.g., the debate whether (Hallett et al. 1994; Stephan et al. 1995; Sabbah et al. 1995; Leonardo et al. 1995; Roth et al. 1996; Porro et al. 1996) or not (Roland et al. 1980; Rao et al. 1993; Decety et al. 1994; Sanes 1994; Parsons et al. 1995) the human primary sensorimotor cortex is activated during imagined movements.

A third approach is to start from both anatomy and function and to fuse the two lines together. A recent development, namely computerized brain atlases (Roland and Zilles 1994) offer the computational tools that are necessary to achieve this goal. On the one hand, genuine microstructural data (e.g., cytoarchitectonic analysis of cell-stained whole brain sections obtained from post-

mortem brains) are brought into the standard anatomical format of a computerized atlas. The degree of interindividual variability can be assessed by importing microstructural data from several brains (approximately 10 in order to keep the time-consuming and cumbersome procedure of microstructural parcellation within reasonable limits). On the other hand, functional imaging data can be brought into the identical standard anatomical format. Both data sets can then be superimposed and correlated with each other on a probabilistic basis. This approach, termed *probabilistic microstructural-functional correlation* opens up the interesting possibility of (1) defining volumes of interest (VOIs) of motor areas that are not based on macroanatomical landmarks but instead on cytoarchitectonic mapping of postmortem brains and of (2) determining in these VOIs changes in regional cerebral blood flow data obtained from PET or fMRI experiments. In the human frontal cortex this new approach has been successfully used so far to map areas 4a and 4p of the primary motor cortex (Geyer et al. 1996) and areas 44 and 45 of Broca's speech region (Amunts et al. 1999) and to correlate microstructural VOIs of these regions with functional data (Geyer et al. 1996; Amunts et al. 1998; Indefrey et al. 1999).

Unfortunately, in humans several anatomical techniques yield poorer results than in the macaque monkey (e.g., immunohistochemistry of neurofilament proteins with the SMI-32 antibody) or cannot be used altogether (e.g., in vivo tract tracing techniques). Hence, a complete multimodal microstructural parcellation of the human isocortical motor system (similar to areas F1 to F7 in the macaque brain) is not yet available. As a consequence, in humans there is still quite a way towards a complete probabilistic microstructural map and, apart from the primary motor cortex, towards firmly establishing homologies between the human and macaque isocortical motor system. Nevertheless, some data do exist and some conclusions can be drawn.

The structural framework

Primary motor cortex

The cytoarchitectonic features and the topography of the human and macaque primary motor cortex are very similar. Also in humans, low cell density, poor lamination, absence of layer IV, a diffuse border between layer VI and the underlying white matter, and giant pyramidal or Betz cells in layer V differentiate the primary motor cortex (Brodmann's area 4; Fig. 9A,B) from the caudally adjoining primary somatosensory cortex. The border lies in the depth of the central sulcus close to its fundus. Scattered or absent giant pyramidal cells and larger, more elongated, and more densely packed pyramids in lower layer III characterize the non-primary motor cortex (Brodmann's area 6; Fig. 9C) that rostrally abuts on area 4. Dorso-medially on the cortical convexity (towards the midline), the rostral border of area 4 lies on

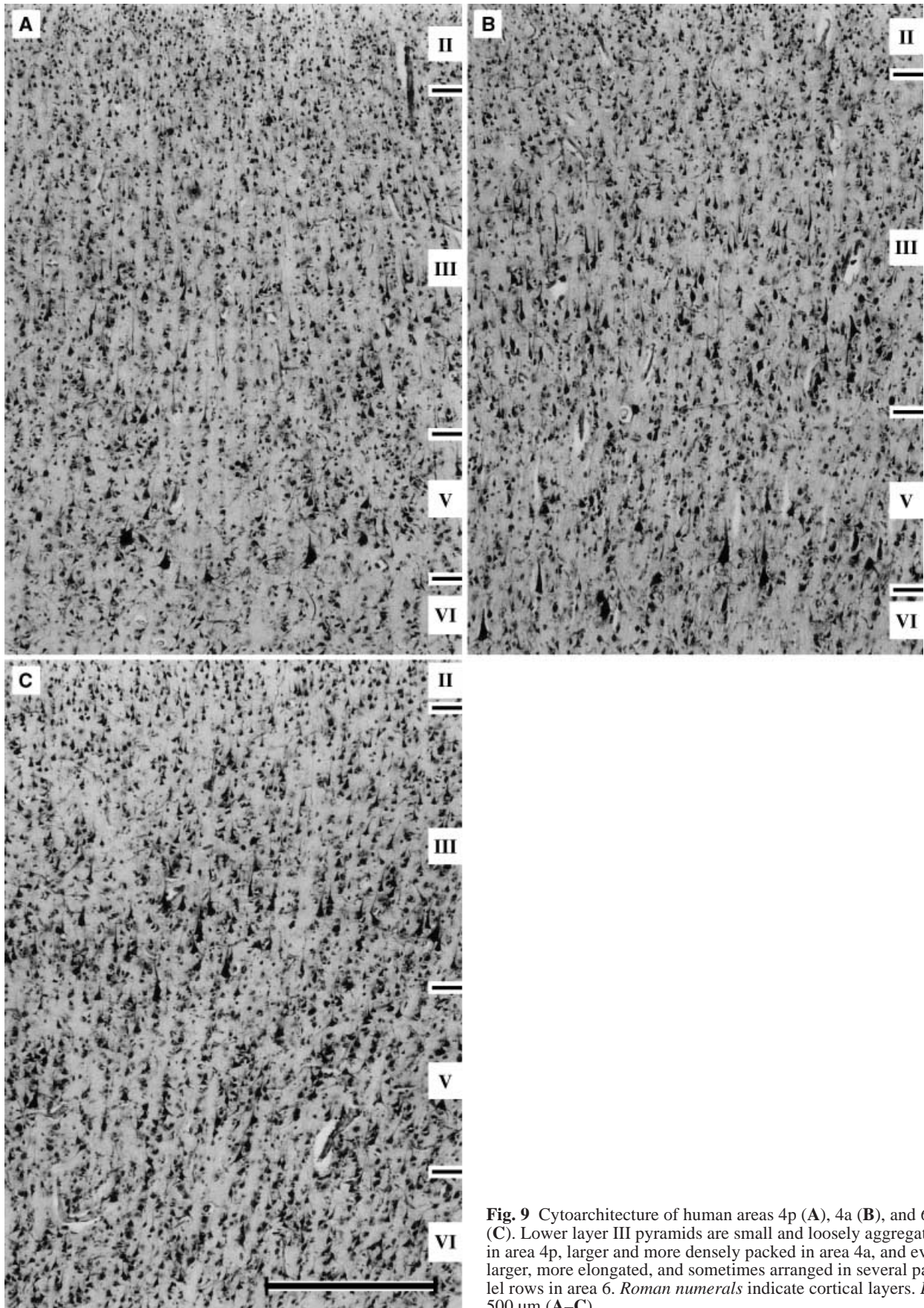


Fig. 9 Cytoarchitecture of human areas 4p (**A**), 4a (**B**), and 6 (**C**). Lower layer III pyramids are small and loosely aggregated in area 4p, larger and more densely packed in area 4a, and even larger, more elongated, and sometimes arranged in several parallel rows in area 6. *Roman numerals* indicate cortical layers. *Bar* 500 μm (**A–C**)

the exposed cortical surface on the vertex of the precentral gyrus. Further ventro-laterally (towards the Sylvian fissure), the rostral border of area 4 recedes in a caudal direction and eventually disappears in the depth of the central sulcus. The mesial part of area 4 occupies the paracentral lobule.

Recently human area 4 has been subdivided into a caudal (area "4 posterior" or 4p; Fig. 9A) and a rostral (area "4 anterior" or 4a; Fig. 9B) region based on differences in cytoarchitecture and neurotransmitter binding sites (Geyer et al. 1996). The two areas are two parallel bands within area 4 running medio-laterally from the midline to the Sylvian fissure. Clear-cut changes in the laminar binding patterns especially of muscarinic cholinergic (revealed with [³H]oxotremorine-M) and serotonergic (revealed with [³H]ketanserin) binding sites closely match corresponding cytoarchitectonic borders. Lower layer III pyramidal cells are small and loosely aggregated in area 4p (Fig. 9A), larger and more densely packed in area 4a (Fig. 9B), and even larger, more elongated, and sometimes arranged in several parallel rows like a phalanx in area 6 (Fig. 9C). There are no obvious differences in size, packing density or arrangement of giant pyramidal cells between areas 4a and 4p. Mean regional binding densities of many neurotransmitter binding sites tend to be higher in area 4p (more similar to the primary somatosensory cortex in which binding densities are even higher; Geyer et al. 1997) whereas they are lower in area 4a (more similar to area 6 in which binding densities are even lower). Hence, there is a clear neurochemical dichotomy within area 4, the posterior part (area 4p) being more similar to the primary somatosensory cortex and the anterior part (area 4a) more similar to the non-primary motor cortex (area 6). At the moment, it is unclear whether there is any homology between human areas 4a and 4p and areas M1r and M1c recently described in the primary motor cortex of the New World owl monkey (*Aotus trivirgatus*) by Stepniewska and coworkers (1993; see above). The topography of areas 4a/4p and M1r/M1c are comparable in both species, but the cytoarchitectonic criteria based on which the two areas have been delineated in each species differ. In addition, should there be any homology (in terms of a common evolutionary ancestor), such a subdivision should also be postulated in the Old World macaque monkey [which is in the evolutionary lineage between the hominoids (i.e., apes and humans) and the New World monkeys]. In macaques, however, no such subdivision has been found so far.

Supplementary motor areas "SMA proper" and "pre-SMA"

Cytoarchitectonic similarities between humans and macaques are also obvious on the mesial cortical surface. Two recent comparative studies (Zilles et al. 1995, 1996) found striking architectonic similarities between macaque areas F3 and F6 and the mesial parts of areas

6a α and 6a β (according to the nomenclature of Vogt and Vogt (1919)), respectively, in humans. Area F3 and mesial area 6a α are characterized by increased cell density in lower layer III and layer V. Both areas are well demarcated on the cortical convexity from area F2 and from lateral area 6a α , respectively. Area F6 and mesial area 6a β are clearly laminated and are characterized by a prominent layer V, well-separated from layers III and VI. Both areas are well-demarcated on the cortical convexity from area F7 and from lateral area 6a β , respectively. Additional similarities have been found on a neurochemical basis (Zilles et al. 1995, 1996; Geyer et al. 1998a). For example, [³H]kainate binding sites are mainly concentrated in the deep layers in both areas in macaques and humans. Binding density in area F3/mesial 6a α is higher than in the primary motor cortex and higher than in the lateral premotor cortex in both species. [³H]oxotremorine-M binding sites show a superficial and a deep cortical band of maximal binding densities in both species. There is a caudo-rostral increase in binding densities from the primary motor cortex to area F6 in macaques and to mesial area 6a β in humans. The authors concluded that human mesial areas 6a α and 6a β are possibly homologous to macaque areas F3 (or SMA proper) and F6 (or pre-SMA), respectively.

In humans, the border between the primary motor cortex and mesial area 6a α (possibly SMA proper) coincides approximately with the VCP line (traversing the posterior commissure vertically to a line that passes through the anterior and posterior commissures). The border between mesial area 6a α and mesial area 6a β (possibly pre-SMA) coincides approximately with the VCA line (traversing the anterior commissure vertically to a line passing through both commissures; Zilles et al. 1996). The coincidence of the borders between the primary motor cortex/SMA proper and the SMA proper/pre-SMA with the VCP and VCA line, respectively has also been shown by Vorobiev et al. (1998). In the latter study, the human SMA proper has been further subdivided into a caudal (SMAC) and a rostral (SMAR) part. Whether these two subdivisions reflect somatotopy or a more fine-grained functional differentiation within the human SMA proper is an unresolved issue at the moment.

In a recent study (Grosbras et al. 1999) a macroanatomical landmark was sought that would indicate the position of the human supplementary eye field (SEF). Such a landmark was indeed found, namely the upper part of the paracentral sulcus on the mesial cortical surface "in the anterior part of the region usually described as the SMA-proper, and posterior to the VCA line, which is usually considered as being the posterior limit of the pre-SMA" (Grosbras et al. 1999, p. 710). This position of the human SEF on the mesial cortical surface is at a clear variance with the position of its monkey homologue on the dorsolateral convexity in area F7. There is no straightforward way to explain this discrepancy. Some clues may be gained from a functional imaging study (Fink et al. 1997) that detected an arm and

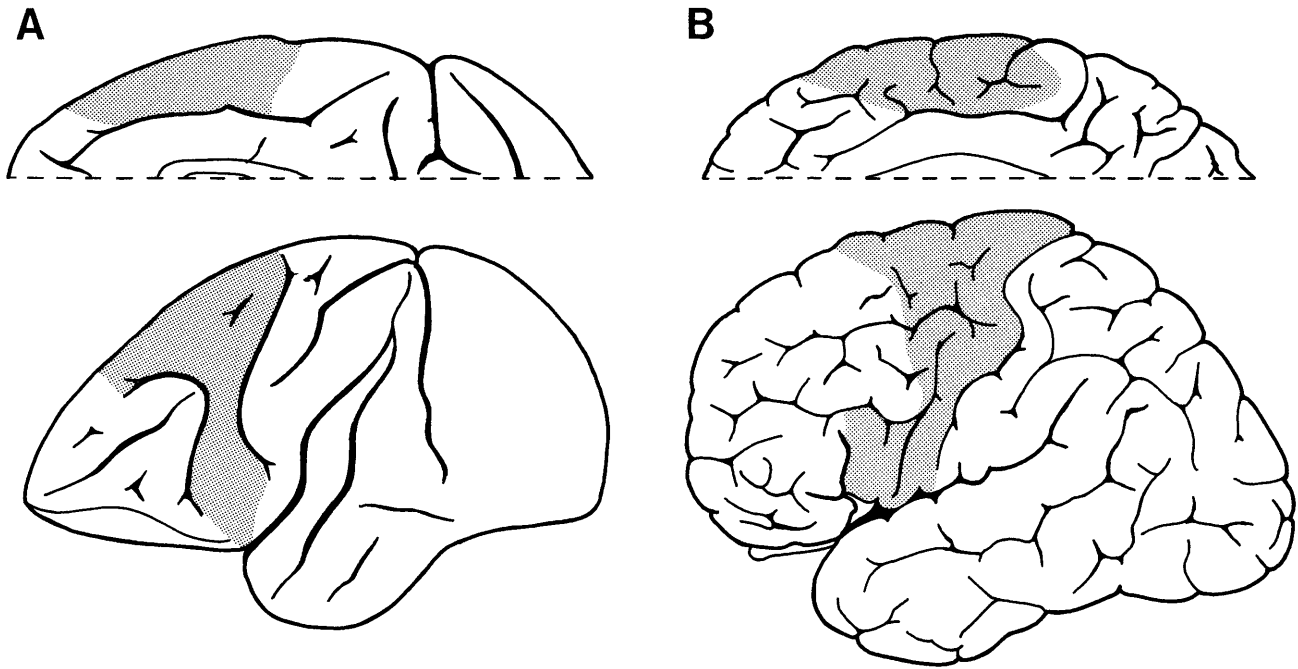


Fig. 10 Extent of the agranular frontal cortex (grey) in the brain of *Cercopithecus* (A), an Old World monkey closely related to the macaque, and in *Homo sapiens* (B). Top part of each figure shows the dorsal part of the mesial cortical surface, bottom part shows the lateral surface. In both species, the border between the agranular frontal cortex and the rostrally adjoining granular prefrontal cortex resembles a mirrored “c”. Maps redrawn from Brodmann (1909)

a leg representation in the human mesial non-primary motor cortex that was confined to the *caudal* half of the region between the VCP and VCA line (which could correspond to area SMAc). Macaque area F3 (or SMA proper) contains a representation of the arm, leg, and face (the latter was not tested in the imaging study). Hence, it might be that only area SMAc is the human homologue of macaque area F3 and area SMAr contains the human SEF that (perhaps due to an evolutionary shift) has moved from a dorsolateral position in the macaque to a mesial position in the human cortex.

Dorsolateral and ventrolateral premotor cortex

On the cortical convexity of the macaque, a conspicuous macroanatomical landmark – the arcuate sulcus – separates the agranular frontal from the granular prefrontal cortex and the border between them looks like a mirrored “c” (Fig. 10A). In the human brain, a comparable sulcus is not evident, but the spatial distribution of the agranular cortex (Brodmann’s areas 4 and 6 plus dysgranular area 44; see below for a further discussion of areas 44 and 45) is strikingly similar. Its rostral border also bears some resemblance to a mirrored “c” (Fig. 10B). In both species the prefrontal cortex extends caudally in the middle of the dorsolateral convexity as if pushing back the agranular cortex, and, conversely, recedes rostrally

in the dorsomedial and ventrolateral parts of the convexity.

In a recent review article (Rizzolatti et al. 1998) an attempt was made to define homologies between the human and macaque dorso- and ventrolateral premotor cortex. Macaque data were compared with data obtained in humans from cytoarchitectonic parcellation (Fig. 1D; Vogt and Vogt 1919), motor representations as determined by electrical stimulation (Fig. 1D; Foerster 1936), sulcal ontogeny (Turner 1948), and the putative location of the human frontal eye field in functional imaging studies (Paus 1996). It was proposed that the superior frontal and superior precentral sulcus (blue in Fig. 1E) represent the human homologue of the macaque superior arcuate sulcus (blue in Fig. 1C). Accordingly, the two areas that occupy the rostral part of the precentral gyrus and the caudal part of the superior frontal gyrus (superior part of area 6 α and area 6 β according to Vogt and Vogt 1919) correspond to macaque areas F2 and F7, respectively. The inferior frontal sulcus and the ascending branch of the inferior precentral sulcus (red in Fig. 1E) correspond to the macaque inferior arcuate sulcus (red in Fig. 1C). The descending branch of the inferior precentral sulcus (green in Fig. 1E) corresponds to the inferior precentral dimple of the macaque monkey (green in Fig. 1C). Accordingly, the inferior part of area 6 α (according to Vogt and Vogt 1919) and area 44 (according to Brodmann 1909) should be homologous to macaque areas F4 and F5, respectively. An open issue is the macaque homologue of human area 45 (according to Brodmann 1909). An area 45 was described in the macaque by Walker (1940) that lies in the rostral bank of the inferior arcuate sulcus and that is related to eye movements (Suzuki and Azuma 1983; Bruce et al. 1985). Human area 45, however, is (together with area 44) the cytoarchitectonic correlate of Broca’s speech

region (Aboitiz and Garcia 1997) and there are no reports in the literature that human area 45 might be involved in eye movements. On the other hand, when one considers the cytoarchitectonic similarities between human areas 44 and 45 and their similar times of myelination onset (cf. Vogt and Vogt 1919), an alternative interpretation would be that human areas 44 and 45 evolved from one and the same area in the macaque monkey, namely area F5.

Functional considerations

As in the macaque, the human primary motor cortex is also organized somatotopically, with the leg being represented on the mesial cortical surface and the trunk, arm, hand, face and throat in a mediolateral sequence on the cortical convexity. Penfield and co-workers showed this arrangement in humans by electrically stimulating the cortical surface in conscious patients undergoing surgery, under local anesthesia, for the removal of tumors, vascular malformations or epileptic foci. The observations culminated in the famous cartoon of the “motor homunculus” that shows, by accordingly distorting the proportions of the body parts, that the largest representations are devoted to the tongue, mouth, hand, and fingers (Penfield and Rasmussen 1952). These findings have been replicated in recent years with functional imaging techniques, e.g., with PET in individual subjects (Fink et al. 1997). Despite an orderly representation of the body’s periphery in each individual subject, topographical variability has been detected across different individuals (Fink et al. 1997). Nonetheless, a macroanatomical landmark exists that reliably indicates the hand area, namely a knob-like structure in the precentral gyrus that looks like an omega or epsilon in the axial plane and that corresponds to the “middle knee” of the central sulcus in postmortem brains (Yousry et al. 1997). As in macaques, somatotopic organization should not be overinterpreted. Also in humans, individual finger movements are represented as multiple and spatially overlapping activation sites (Sanes et al. 1995). Activation within the caudal bank of the precentral gyrus (or rostral bank of the central sulcus) has been detected in many PET and fMRI studies by using a wide variety of different motor paradigms. Since the foci of activation were related to macroanatomical landmarks (and not to microstructurally defined cortical areas) none of these studies could exclude that the foci also extended (at least to some extent) into the rostrally adjoining area 6. In a recent study, PET foci were correlated with the population maps of areas 4a and 4p of the primary motor cortex as obtained from cytoarchitectonic analysis of postmortem brains (probabilistic microstructural-functional correlation, cf. above). It was found that roughness discrimination of two cylinders with different microprofiles activated area 4p significantly more than did a control condition of self-generated movements (Geyer et al. 1996). Neurochemically, area 4p is more similar to the primary somatosensory cortex, whereas area 4a is more

similar to the non-primary motor cortex (area 6). This difference seems to be reflected on a functional level in such a way that a voluntary motor act that is closely modulated by somatosensory feedback (i.e., scanning the texture of a surface) leads to a stronger activation of area 4p.

Area 4 contains a somatotopic representation of the body’s periphery. In the macaque, additional motor maps (i.e., somatotopic representations) are present in the SMA proper (area F3), the PMd (area F2), and the PMv (areas F4 and F5; cf. Fig. 1A,C). In a recent functional imaging study in individual subjects (Fink et al. 1997), additional motor maps were also detected in humans: on the mesial cortical surface rostral to the primary motor leg representation (probably corresponding to the SMA proper), on the dorsolateral convexity around the superior precentral sulcus (probably corresponding to the PMd), and a third map on the ventrolateral convexity in the frontal operculum (possibly corresponding to the PMv). Thus, a similar organizational principle also seems to exist in the human non-primary motor cortex.

However, since the microstructural framework is still poorly established in humans, we think it is more appropriate to discuss some functional *gradients* across this region that have emerged from recent imaging studies rather than to speculate about specific “functions” of non-primary motor areas (see also Passingham 1997).

Functional gradients in a rostro-caudal direction

Complexity of movements Motor tasks can be classified as “simple” or “complex” depending on the spatial and/or temporal organization of the movement. Picard and Strick (1996) classified as “simple” those tasks that require the most basic spatial or temporal organization of movement or tasks that are overlearned and highly practiced (e.g., moving a joystick in a fixed direction after an auditory trigger signal). Complex tasks are characterized by additional motor or cognitive demands such as the selection of a motor response or the acquisition of a conditional association (e.g., moving a joystick in a random, self-selected direction). On the mesial cortical surface, most regions activated during the execution of simple tasks are located caudal to the VCA line (possibly within the SMA proper), whereas most regions activated during relatively more complex tasks are located more rostrally (typically rostral to the VCA line; possibly within the pre-SMA; Picard and Strick 1996). In a free-selection task (FREE) subjects were required to freely select between four movements each time they heard a pacing tone. In a repetitive task (REP) the subjects had to make the same movement on all trials. The subjects either moved a joystick in one of four directions (Deiber et al. 1991; Playford et al. 1992) or they selected between movements of the four fingers (Jueptner et al. 1997a). Contrasting the FREE versus the REP condition showed activity rostral to the VCA line (see also Passingham 1997). Such a gradient is also obvious on the lateral surface. The same comparison (FREE vs. REP) activated regions rostral to

(Deiber et al. 1991) or around (Jueptner et al. 1997a) the VCA line. In another set of experiments subjects were scanned while they freely selected between four finger movements (FREE), performed a prelearned sequence of the four finger movements (PRE) or during a baseline condition without any movements (BASE). On the lateral surface, strong activity was found during the free selection task (FREE vs. BASE) whereas during the prelearned task (PRE vs. BASE) the activation lay more caudally, close to the border with the primary motor cortex (Jueptner et al. 1997a,b). The results suggest that both on the mesial and on the lateral surface there is a functional gradient related to the complexity of movements; i.e., relatively more complex movements engage more rostral regions (typically anterior to the VCA line) whereas simpler movements activate more caudal regions.

Motor learning A similar gradient has also been revealed for learning a new sequence of motor acts as compared to performing a highly automatic sequence. Conceptually, this is related to the complexity of movements since motor learning imposes a higher cognitive demand on the subject than performing an overlearned sequence. In a study by Jenkins et al. (1994) subjects learned with four fingers of the right hand a new sequence of keypresses, eight moves long, by trial and error (NEW). In the prelearned condition (PRE) they performed a sequence learned before scanning. Learning the new sequence (NEW vs. PRE) activated the lateral premotor cortex rostral to the VCA line. A similar learning study by Jueptner et al. (1997b) also found activation in the lateral premotor cortex extending up to and slightly rostral to the level of the VCA line. When comparing automatic performance with new learning (PRE vs. NEW), Jenkins et al. (1994) found activity on the mesial cortical surface with a peak caudal to the VCA line. The peaks for automatic performance in the study by Jueptner et al. (1997b) lay caudal to the VCA line both on the mesial and the lateral cortical surface. In conclusion, an increasing degree of practice on a motor task shifts the activity more caudally, i.e., towards the primary motor cortex.

According to Passingham (1997) the functional implications of the rostro-caudal gradients are that more anterior cortical regions are engaged only when the task is *nonroutine*, e.g., when the subjects must make new decisions. Such decisions may require attention, memory of recent information, or preparation for future responses. In such circumstances, cortical regions are activated that are less directly linked with the primary motor cortex.

Functional gradients in a medio-lateral direction

Medio-lateral gradients are more difficult to reveal than are gradients in a rostro-caudal direction. The concept gained from electrophysiological studies in macaques that the SMA proper and pre-SMA are more important for self-initiated movements based on internal cues whereas the dorso- and ventrolateral premotor cortex are

more involved in triggering and guiding movements by external cues has not been supported by imaging studies in humans. In the study by Deiber et al. (1991, see above) a free-selection task (FREE) was compared with a repetitive task (REP). The comparison "FREE vs. REP" showed activity on the mesial but also on the lateral cortical surface. In the study by Jenkins et al. (1994, see above) learning a new sequence of movements (NEW) was compared with a prelearned sequence (PRE). The comparison "NEW vs. PRE" showed *higher* activity on the lateral than on the mesial cortical surface.

Open loop and closed loop performance This new concept has recently been introduced by Passingham and co-workers (Toni et al. 1997; Passingham 1997). Subjects were scanned four times while they learned a visual conditional task and a motor sequence task: in the initial phase of learning (scan 1), during intermediate stages (scans 2 and 3), and when the task was highly practiced (scan 4). The four fingers of the right hand lay on keys, and at each pacing cue the subject moved one of them. The subjects learned the sequence by using feedback cues. In the sequence task, visual nonsense shapes were used as pacing cues, and the feedback cues were a "tick" on the screen if the response was correct and a "cross" if it was incorrect (i.e., the subjects learned by trial and error). In the visual conditional task the pacing cues also served to instruct the subjects which finger to move. Each nonsense shape specified one particular finger. The lateral premotor cortex was equally activated during learning of either task (scans 1 and 2). A difference between the two tasks, however, was found in scans 3 and 4, when the task had become highly practiced. There was significant activity on the mesial cortical surface for the sequence task but not for the visual conditional task. The results were interpreted in the following way (Toni et al. 1997; Passingham 1997). During new learning of both tasks, performance can be described as *closed loop*, i.e., the subject must pay close attention to the outcomes. During overlearned performance of the sequence task, performance is *open loop*, i.e., the subjects know in advance which movements to make and no longer have to pay attention to the outcomes. On the other hand, overlearned performance of the visual conditional task remains *closed loop* since the subjects must always respond to the particular visual cue that is presented on any trial.

In summary, the emerging functional implications of a medio-lateral gradient suggest that the lateral premotor cortex is activated when a task is learned and the task is closed loop (even when it is a sequence task). The mesial cortical surface is particularly activated during open loop performance of a sequence task.

Acknowledgements This work has been supported by grants from the Deutsche Forschungsgemeinschaft (SFB 194/A6), from the European Union under the BioMed 2 and BioTech programs, and from the US National Institute of Mental Health (International Consortium of Brain Mapping). Thanks are due to Ursula Blohm, Renate Dohm, Nadine Ivens, and Brigitte Machus for continuous encouragement and excellent technical assistance and to Birgit Jansen for expert help with the photography.

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