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# **Human premotor cortex: Beyond motor performance**

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## **Bibliographische Beschreibung**

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Die vorliegende Schrift zur kumulativen Habilitation befasst sich mit den noch wenig untersuchten nicht-motorischen Funktionen des humanen prämotorischen Cortex. Berichtet wird eine Serie von Experimenten, die an gesunden jungen Probanden mittels funktioneller Magnet-Resonanz-Tomographie durchgeführt wurden, und deren übergreifende Fragestellung war, welche Faktoren die Aktivität prämotorischer Subregionen bei der rein attentionalen Verarbeitung sequentieller Information signifikant beeinflussen.

Im ersten Teil der Habilitationsschrift wird die thematisch relevante tierexperimentelle Literatur, insbesondere anhand von Einzelzellstudien am Makaken, aufgearbeitet und zusammengefasst. Aus dieser Forschung konnten für die vorliegende Arbeit wesentliche Anregungen gewonnen werden, da sie sich besonders im vergangenen Jahrzehnt verstärkt um die Aufklärung nicht-motorischer Funktionen des prämotorischen Cortex beim Affen bemüht hat. Aktuelle Befunde zur Struktur, zu den Hauptprojektionen und den physiologischen Charakteristika weisen gleichermaßen auf eine Parzellierung des prämotorischen Cortex des Affen hin, die das klassische Brodmann Areal 6 in mindestens sieben funktionell wie anatomisch heterogene Felder verfeinert. Die funktionellen Befunde legen nahe, dass die Vorbereitung von Bewegung lediglich ein kleiner Ausschnitt der prämotorisch unterstützten Funktionen ist.

Der zweite Teil der Arbeit rekonstruiert die aktuellen strukturellen und funktionellen Befunde zum humanen prämotorischen Cortex. Beide Bereiche - Struktur und Funktion - haben in den letzten Jahren durch das Aufkommen neuer Untersuchungsmethoden einen gewissen Zuwachs an Informationen zu verzeichnen, ohne diese jedoch bereits in eine funktionell-neuroanatomische Beschreibung integrieren zu können. Insbesondere steht der Großteil funktioneller Ergebnisse aus der Bildgebung praktisch isoliert von den umfangreicheren und weiter entwickelten tierexperimentellen Daten und Modellen, ohne von diesen zu profitieren. Eine systematische Untersuchung prämotorischer Funktionen mittels Bildgebung bzw. Patientenstudien existiert nicht. Vor diesem Hintergrund wird das eigene in der Bildgebung angesiedelte Forschungsprojekt motiviert und eingeführt.

Der dritte Teil umfasst eine Skizze des eigenen Forschungsprojekts. Dargestellt werden die wesentlichen Fragestellungen und Befunde aus peer-review Publikationen von 11 fMRT-Studien und einer Patientenstudie. Die Befunde lassen sich in drei Aussagen gliedern: (1) Der prämotorische Cortex unterstützt prospektive sensorische Aufmerksamkeit bzw. Repräsentation. Nicht die Anwesenheit oder faktische Detektierbarkeit von sequentiellen Reizstrukturen, sondern allein der Versuch ihrer Vorhersage führt zu einer Aktivität dieses Cortex. (2) Die prämotorischen Korrelate prospektiver sequentieller Verarbeitung organisieren sich, in Abhängigkeit von der beachteten Reizeigenschaft, gemäß einer groben Somatotopie, die derjenigen des Primären Motorischen Cortex entspricht. Die robust replizierten Befunde werden als habituell-pragmatische Körperkarte (habitual pragmatic body map) interpretiert: Eine Reizeigenschaft wird demnach stets auf dasjenige prämotorische Areal abgebildet, das dem habituell passenden motorischen Effektor zugeordnet ist. (3) Die Bandbreite von Stimuli, auf die der prämotorische Cortex unter prädiktiver Instruktion anspricht, legt eine hoch fragmentarische eigenschaftsbasierte Repräsentation nahe, deren Kombination beliebige aktuelle Umwelten darstellen kann.

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## **Part I**

# **Premotor cortex in non-human primates**





# Chapter 1

## Introduction

The function traditionally attributed to the premotor cortex (PM), no matter whether in man or in monkey, is the preparation and organization of movement and action (Wise, 1985). However, with the introduction of imaging methods, which allow the neural correlates of behavioral functions to be measured on-line, premotor activations have frequently found in non-motor "cognitive" domains. As these findings were difficult to interpret in light of the classical "motor" view, they were typically taken to reflect some kind of latent motor processes. As such, they were experimental artifacts of either non-suppressible or deliberately chosen behavioral strategies such as e.g. verbalizing or tapping, or simply movement noise. However, nowadays the exploration of cognitive function of the human premotor cortex has become an independent field of research, supported and also inspired by results from research in the monkey. Currently, a diversity of concepts on premotor functions co-exist, partly referring to the classical motor account, partly to the scope of non-motor functions.

Imaging findings in humans are of limited value unless they are integrated with the current knowledge base on brain function and anatomy derived from other findings and methods. This applies particularly to the integration of human data with findings from non-human primates studies which provide what is almost completely missing in humans: a detailed knowledge about connectivities, single cell computations, and cortical-subcortical network functions. Potential benefit is reciprocal: Hypotheses on function and network relations can be derived from monkey research, and conversely, human findings can be re-tested in monkeys using appropriate experimental paradigms. In this first chapter, structure, connectivities, and physiological features of the frontal cortical motor areas of the non-human primate will be summarized. Each section will be introduced by an outline of the most important methods and techniques that are typically employed in studies on the monkey premotor cortex.



## Chapter 2

# Structure

### 2.1 Staining and labeling techniques

#### Histology

Cytoarchitectonic studies are based on the analysis of structural inhomogeneities in nervous tissue. Boundaries of brain regions are established where local structural properties such as numerical cell density, size, shape or orientation change. In addition, when the number of layers is considered, borders are identifiable where different layers merge, subdivide, or change with regard to their markedness. Today, these properties are measured with automatic devices from histological sections. In the last few years, image analyzers have been used to measure observer-independent the perikarya-neuropil-ratio, or gray level index (GLI) (Schleicher & Zilles, 1990), a profile describing the cytoarchitecture in several features or feature vectors.

The most frequently used staining technique is Nissl staining which visualizes dendrites and cell bodies (perikarya), and Myelin staining which visualizes axons (which become myelinated upon entering the white matter where they form the ascending and descending tracts of the spinal cord). Especially for defining cortical fields, borders between two myeloarchitectural types are sharper than transitions in cytoarchitecture, because different patterns of tangential and radial distribution of myelinated fibers within the cortex are often more conspicuous than cellular inhomogeneities. Therefore, within one study different staining techniques are usually applied on alternating sections.

**Nissl staining** is used to demonstrate the Nissl granules of the nerve cell bodies. Nissl bodies are groups of ribosomes that are produced by the nucleolus and which are necessary for translation of genetic information into proteins (protein biosynthesis). Substances used for Nissl-staining are basophilic dyes such as cresyl fast

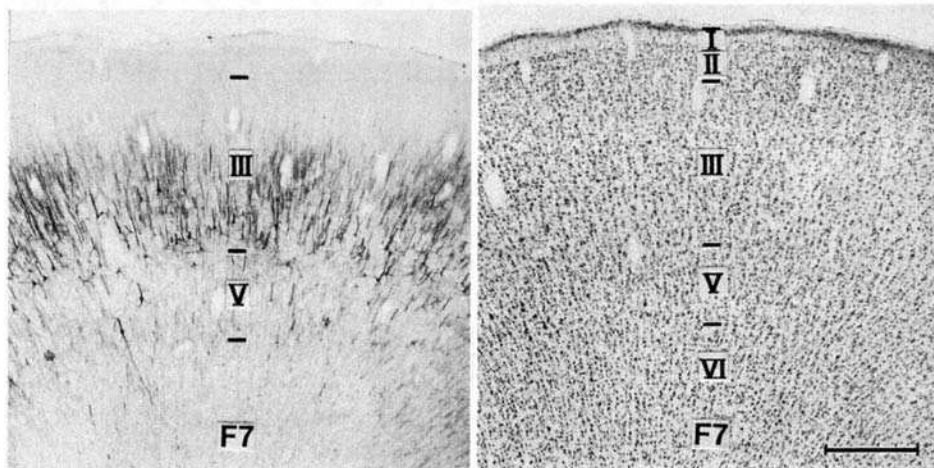


Figure 2.1: *Distribution of SMI-32-immunoreactive neurons and cytoarchitecture in an adjacent Nissl-stained section (Geyer et al., 2000)*

violet, methylene blue, toluidine-blue, thionine and hematoxylin. Nissl-staining is often used in combination with silver staining which demonstrates not only nerve cell bodies, but also large cell processes and fiber tracts by reacting with the neurofibrillar content.

**Myelin staining** identifies the lipid of Myelin sheaths, a specialized membrane of lipoprotein that is wrapped around most axons and long dendrites in the nervous system that propagates the action potential. Often used in myelin demonstration is luxol fast blue (methanol fast blue), a group of copper phtalocyanine dyes which can be combined with Nissl staining and other techniques.

### Histochemistry

Histochemistry is a staining that can be used to identify specific chemical or enzyme components in cells. Three methods have to be distinguished: enzyme histochemistry, autoradiography, and immunohistochemistry.

**Enzyme Histochemistry** The most popular technique used in enzyme histochemistry is cytochrome oxidase (CO) (Wong-Riley, 1989). CO is an integral transmembrane enzyme that is found in the inner mitochondrial membrane. Because it acts to catalyze the generation of adenosinetriphosphate (ATP), an energy

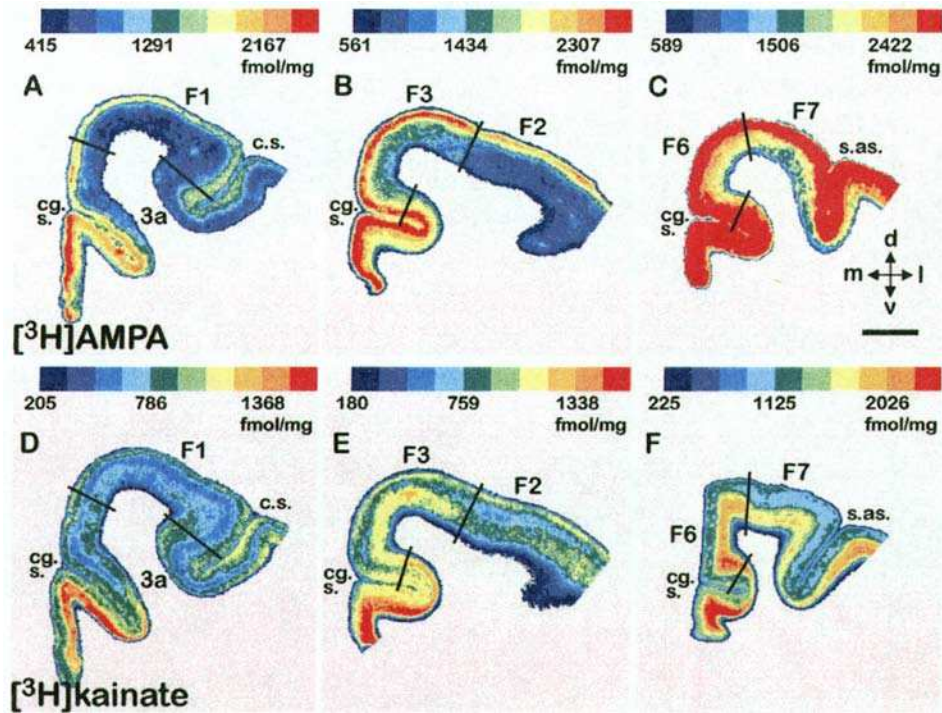


Figure 2.2: Receptor autoradiographs showing color-coded binding sites. The changes in laminar distribution patterns of binding sites which coincide with cytoarchitecturally defined borders of F-fields are marked (Geyer et al., 1998).

molecule, the amount of CO in a cell or nucleus can be used as an indicator of cellular activity. Apart from its use as an activity indicator, however, CO labeling reveals arrays of CO-rich and deficient regions, so-called blobs and interblobs. This enzyme architecture presumably reflects stable differences in energy consumption in two populations of neurons. Dense CO staining is most visible in cortical layers IIIb, IVa and IVc, but also cells directly above and below blobs and interblobs appear to show corresponding differences in connectivity and functional characteristics (Yoshioka et al., 1996).

**Transmitter receptor autoradiography** is used to visualize radio-isotopes bound to solid targets using a radiation-sensitive film or photoemulsion layer (Sovago et al., 2001). In receptor (or radio-ligand) autoradiography (RA), natural or synthetic ligands which are capable of binding to specific receptors are labeled with radioactive isotopes, so that their sites of deposition and binding can subse-

quently be detected. The most commonly used form of RA in neuroscience is light microscopic autoradiography performed *in vitro* on small tissue sections. It provides anatomical data with high spatial resolution images ( $< 100 \mu\text{m}$ ) (Sharif & Eglén, 1993). The number of receptor binding sites and the affinity of the radioligand for its receptor are quantified by densitometric methods with the aid of computerized image processing systems. RA allows the fate of bioactive compounds in tissues, cells and subcellular elements to be traced at selected time points, and hence is a histochemical technique that adds functional and time-related information to the structure.

**Immunohistochemistry** is an amalgamation of immunology and histology that gives information about the ability of a particular tissue to express an antigen and the exact cellular localization of the antigen. The immunohistochemical staining of (nonphosphorylated epitopes on) the neurofilament protein triplet with the (monoclonal) antibody SMI-32 is a microstructural technique to map areas in the primate cortex (Sternberger & Sternberger, 1987; Lee et al., 1988). SMI-32 immunoreactivity is confined mainly to somata and dendrites of cells in which neurofilament proteins are found, and these are the pyramidal cells in layers III and V (Campbell & Morrison, 1989; Hof & Morrison, 1995; Hof et al., 1995). Since the laminar pattern of neurofilament expression varies markedly between regions of the primate cortex, SMI-32 has proven useful for delineating cortical areas (Carmichael & Price, 1994; Chaudhuri et al., 1996). Neurofilament architecture provided by such immune stains is often combined with cytoarchitecture (Nissl staining), myeloarchitecture (Gallyas method), and enzyme architecture (CO) in order to cross-validate findings. Immune stains can distinguish many cortical regions whose boundaries are not readily discernible on the basis of the Nissl stain (Hof & Morrison, 1995, cf. Figure 2.1).

## 2.2 Structural parcelling

Today's prevailing structural parcelling of the agranular frontal isocortex of the macaque monkey is into seven areas according to the F-nomenclature ("F" for "frontal"). This parcelling is based on histochemical data (Matelli et al., 1985) and has been confirmed and refined with other techniques such as cytoarchitecture (Matelli et al., 1991), receptor autoradiographic mapping (Zilles et al., 1995), and immunohistochemical staining (Petrides & Pandya, 1994; Preuss et al., 1997; Gabernet et al., 1999; Geyer et al., 2000b). Seven F-fields make up the frontal motor isocortex, with higher numbered fields generally located anteriorly to those with lower numbers (Figure 2.3). The medial premotor cortex is subdivided into F3 (supplementary motor area or SMA proper) and F6 (preSMA); the

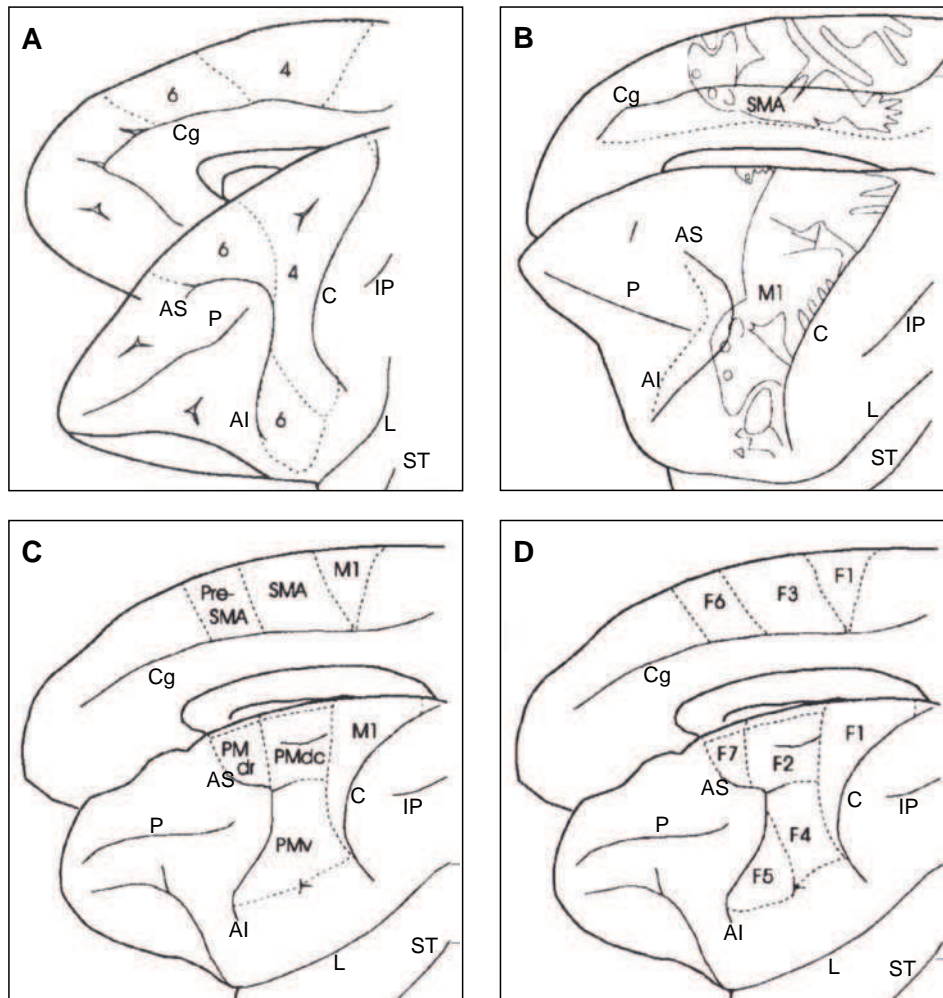


Figure 2.3: Subdivisions of the agranular frontal cortex in the monkey according to A: Brodmann (1909), B: Woolsey et al. (1952) and C/D: Matelli et al. (1985) (modified from Luppino and Rizzolatti, 2000).



dorsolateral premotor cortex is made up by areas F2 and F7, the ventrolateral by areas F4 and F5; finally primary motor cortex (MI) is referred to as area F1. Based on structural and functional properties, several of these F-fields have been recently further subdivided, for instance F5 into areas F5ab and F5c, and area F2 into F2v and F2d. Generally, immunolabeling is maximal in the caudal agranular frontal cortex and decreases in several fairly abrupt and step-like changes caudo-rostrally towards the prefrontal cortex (Gabermet et al., 1999; Geyer et al., 2000b). Particularly, MI and PM can be distinguished by an abrupt loss of labeled pyramidal cells in layer V and a decrease of immunoreactivity in layer III. In this way, also dorsal premotor cortex (PMd) and MI can be distinguished with ease. In contrast, PMv contains a large number of SMI-32 positive cells in layer V, resembling MI more strictly. However, ventral premotor cortex (PMv) and MI can be distinguished by the decrease in size and density of layer V and layer III pyramidal cells (Figure 2.4).

F6	F3	F1
Clearly laminated; dark layer V well demarcated from layers III and VI; incipient layer IV at the rostral border	Poor lamination, increased cellular density in lower layer III and upper V; scattered giant pyramidal cells only at the border to F1	Poor lamination, low cell density, absent layer IV, very prominent giant pyramidal cells in layer V.
F7	F2	
Clearly laminated, prominent layer V; cellular density comparable to that in F6 but pyramidal cells smaller	Poor lamination, scattered giant pyramidal cells only at the border to F1; cell density in III and V slightly lower than in F3. Ventral F2v and dorsal F2d separated only by layer V immunoreaction.	
F5	F4	
Clearly laminated, prominent layer V; cellular density higher than in F4;	Poor lamination, scattered giant pyramidal cells at the border to F1 and F2; cell density lower than in F2	

Figure 2.4: *Structural differences between the seven premotor F-fields as defined in the monkey.*



## Chapter 3

# Connectivity

Connections to and from the frontal motor isocortex are confusing and complex. However, reduced to their basic components, they can greatly improve our understanding of how the premotor cortex enables us to perform such a variety of behaviors. Though the isolated analysis of a cortical region is often the only way to progress in research, it is crucial to keep in mind which network components add to the effects. A finding that has dramatically changed the view on motor organization is that reciprocally connected premotor and parietal areas often share neurons with similar properties, suggesting widely distributed representations. This chapter gives an insight into premotor networks that have been intensively investigated within the last two decades.

### 3.1 Tracer techniques

Capitalizing on the bi-directional transmission of material between the soma and the axon terminals, anterograde tracers are used to identify afferent projections into a target area (from cell body to axon terminal), whereas retrograde tracers are used to identify efferent projections from the origin area (from the axon terminal to the cell body) (Mesulam, 1982; Kuypers & Huisman, 1984; Kobbert et al., 2000). Tracers used for retrograde tracing are e.g. the plant enzyme horseradish peroxidase (HRP) and fluorescent dyes like fast blue, more recently also fluoro-gold or mini ruby and others. Tracers used for anterograde tracing are e.g. radioactively labeled amino acids and fluorescent dyes; more recent classes are plant lectins and dextran amines. Some tracers can be used for both directions, e.g. HRP conjugated with wheat-germ agglutinin (WGA-HRP) with enhanced uptake and rapid transport. For functional studies, a beforehand identification of the functionally relevant area is often achieved by intracortical microstimulation (electrophysiological mapping) (e.g. Gentilucci et al., 1988, see also chapter 4).

The tracer is introduced into the tissue using pressure injection, iontophoretic injection, or mechanical insertion of dye crystals. Tracers enter axons or dendrites by active uptake, either via nerve terminals or via injured neuritic profiles, or by passive diffusion into neurons due to a local concentration gradient. Within the cell, tracers are subsequently transported either actively in vesicles or by lateral diffusion within the plane of the membrane. Following appropriate survival time for the tracer to be transported (this varies according to the tracer used and the distance of the neuronal circuitry under investigation) the tissue is collected and subsequently analyzed. Whereas fluorescent tracers are directly visible in fluorescent light, other tracers are detected with specific antibodies that are subsequently visualized with immunohistochemical methods.

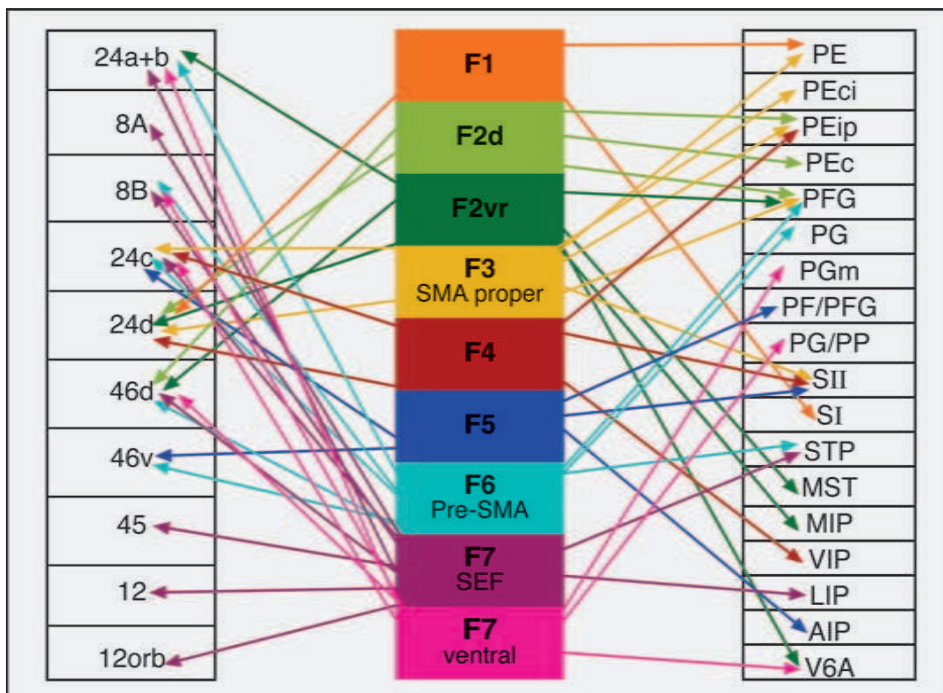


Figure 3.1: Overview of the extrinsic and intrinsic connections of the premotor cortex.

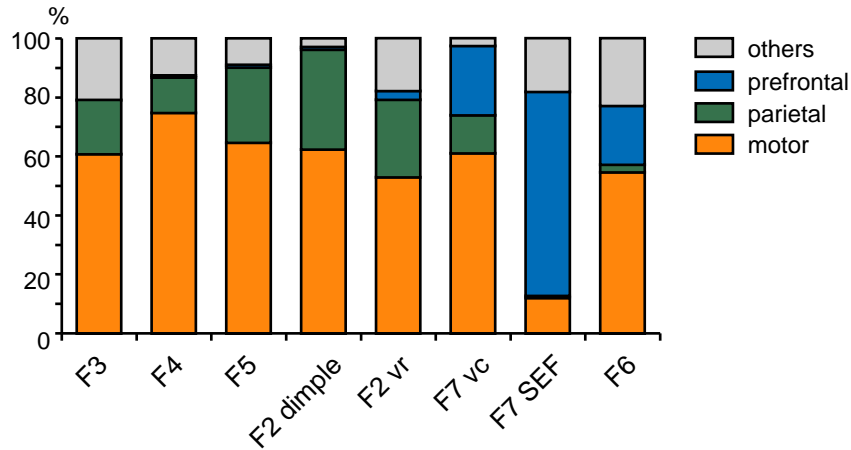


Figure 3.2: *Quantitative analysis of intrinsic and extrinsic connections of the pre-motor areas in the macaque monkey (Matelli & Luppino, 2001).*

### 3.2 Main projections

The motor areas rostral to F1 are selectively linked to one another (intrinsic connections), as well as with the prefrontal cortex and the parietal lobe (extrinsic connections, Matelli et al., 1986; Barbas & Pandya, 1987; Dum & Strick, 1991; Luppino et al., 1993; Lu et al., 1994). An overview of premotor and primary motor connections is given in Figure 3.1. The generally extensive intrinsic connectivity of the motor cortices is suggested to be due to the associative character of this area and possibly its role in sequential motor acts (for instance in the simultaneous preparation of hand and mouth in a coordinated hand-mouth sequence). Accordingly, except for F1, intrinsic projections connect the lateral F-fields across somatotopically different regions (Matelli et al., 1984, see also chapter 4.2.2), linking for instance mouth to hand, and hand to leg representations (Ghosh & Gattera, 1995). However, whereas interconnections within PMv and PMd are profuse, there are only sparse connections between PMv and PMd, a finding that points to distinct functional roles of these two premotor subareas (Kurata, 1991; Ghosh & Gattera, 1995). Furthermore, medial and lateral premotor areas also build two projection families. Medial area F3 receives somatotopically organized afferents from F1, F2, F4, and F5, whereas medial area F6 receives input mainly (or perhaps exclusively) from area F5 (Luppino et al., 1990). Finally, there are no significant connections between either F3 or F6 and field F7.

With respect to extrinsic connections, two classes of F-fields can be dissociated upon their main projection characteristics. Interestingly, the same two classes

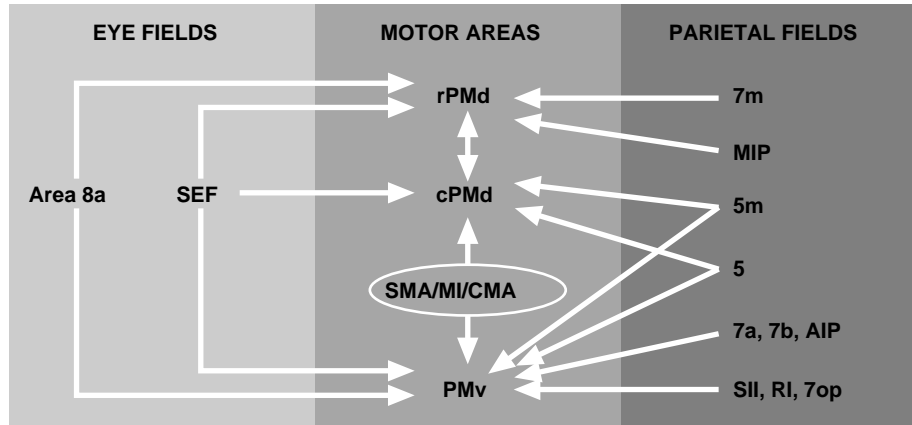


Figure 3.3: *Schema of the connections of dorsal and ventral premotor cortex with other motor areas and with the parietal lobe (modified from Ghosh and Gattera, 1995).*

differ also with regard to their connections with F1 and their corticospinal projections. On the one hand, the anterior fields F6 and F7 are prefronto-dependent and have diffuse connections with all other motor areas except for area F1 (Barbas & Pandya, 1987; Luppino et al., 1990, 1993; Lu et al., 1994). On the other hand, the posterior fields F2, F3, F4, and the anterior-ventral field F5 are parieto-dependent and have somatotopically organized connections with F1 (Matsumura & Kubota, 1979; Muakkassa & Strick, 1979; Matelli et al., 1986; Luppino et al., 1993). Parietal projections are much stronger<sup>1</sup> for PMv than for PMd and involve more anatomically and functionally differentiated parietal regions (Ghosh & Gattera, 1995, see Figure 3.3). Hence, like their intrinsic connections, extrinsic connections of PMv and PMd point to different functional profiles. F6 and F7 project to the brain stem, whereas F2, F3, F4, and F5 (as well as F1) send direct projections to the spinal cord (Keizer & Kuypers, 1989; He et al., 1993; Galea & Darian-Smith, 1994; Luppino et al., 1994; He et al., 1995)<sup>2</sup>. Partly confirming this grouping, recent findings indicate that there are four thalamo-premotor projection families, each of which receives inputs from a specific set of thalamic nuclei: F1, F2 and F3, F6 and F7, and finally F4 and F5 (Rouiller et al., 1999).

Functionally most important, premotor and parietal areas are reciprocally con-

<sup>1</sup>“Strength” of connections refers to the number of projecting neurons, whereas the number and the location of synapses of terminal axons are neglected.

<sup>2</sup>About 30-50% of corticospinal fibers originate from F1 and 10-30% from PM (the remaining projections spring from the parietal lobe) (Russel & DeMeyer, 1961; Murray & Coulter, 1981; Toyoshima & Sakai, 1982).

nected in multiple parallel circuits (see section 4.4.1) whose segregation supports their functional differentiation (Tanne-Gariepy et al., 2002). Connections of the premotor areas will be outlined in more detail in the following, whereas those of the primary motor cortex will be largely omitted here. It should only be noted that F1 receives cortical afferents from SMA, the cingulate motor area (CMA, area 24), the lateral premotor cortex, the primary and the secondary somatosensory cortex (SI and SII), as well as from parietal areas 5 and 7 (Godschalk et al., 1984; Leichnetz, 1986; Ghosh et al., 1987; Tokuno & Tanji, 1993).

**Medial premotor cortex (F3 and F6)** F6 receives cingulate input (about 20%) from areas 24a, 24b, and 24c, prefrontal input (about 20%) from areas 46 and 8B, temporal and parietal input (5%) from area PFG (parietal areas PFG, part of area 7), PG (parietal area 7a), and STG (superior temporal gyrus). Intrinsic input originates from area F5 and F7 (about 40%), from F2, F3, and F4 (about 15%), but not from F1. In contrast, F3 receives cingulate input (about 20%) from areas 24c and 24d, and parietal input (about 20%) from areas PE (parietal areas PE, part of area 5), PEci (cingulate PE), SI, SII, and PFG; frontal input originates from area F2 and F4 (about 25%), areas F5, F6, and F7 (about 20%), and F1 (about 15%). Main thalamic input dissociates F3 and F6 (Matelli & Luppino, 1996; Rizzolatti et al., 1996). The nucleus ventralis anterior pars parvocellularis (VApc, also known as area X (Olszewski, 1952)) projects to F6, bearing information from caudate nucleus and cerebellum (Alexander et al., 1986; Rouiller et al., 1994). Main thalamic input into F3 comes from the nucleus ventralis lateralis pars oralis (Vlo) which bears information from the putamen.

**Dorsal premotor cortex (F2 and F7)** F2 is dissociated in two subareas, one peri-arcuate or ventrorostral field, which is located ventrally to the superior precentral dimple (F2pa, F2v, F2vr) and one precentral dimple or dorsal field, which is located dorsally to the superior precentral dimple (F2pre-CD, F2d) (Geyer et al., 2000b; Rizzolatti & Luppino, 2001). Both F2 subareas receive cingulate input from area 24d, and F2vr also from area 24a and 24b. For both, there is no (Geyer et al., 2000a) or low (Rizzolatti & Luppino, 2001) prefrontal input from area 46d. Both possibly receive small parietal input also from area PFG. For F2vr, main parietal input terminates from area MIP (medial intraparietal area, part of area 5) and area V6A (visual area 6A, part of area 19) ("MIP/V6A - F2v circuit"). For F2d, parietal input comes from area PEc (caudal part of PE) and PEip (part of PE that lies within the intraparietal sulcus, that is, the anterior part of area PEa) ("PEip/PEc - F2d circuit") (Marconi et al., 2001), and temporal input from area MST (medial superior temporal area). F2d receives input from F4, and to a lesser extent from F7 and F3. F2vr receives input from F5, and to a lesser extent from



F7, F4, F6, and F3 (Marconi et al., 2001). F2 has connections with F1. Like F2, F7 is dissociated in two subareas, one dorsal (F7d, supplementary eye field, SEF (Schlag & Schlag-Rey, 1987)) and one ventral (F7v). Both receive cingulate input from area 24a, 24b, and 24c, and prefrontal input from 8B and 46d. F7d/SEF receives additional prefrontal input from area 8A, 45, 12, and 12orb. This area receives parietal input from area LIP (lateral intraparietal area, part of area 7) ("LIP - F7d circuit"), and temporal input from STG, whereas F7v receives parietal input from area PGm (mesial part of area 7) ("PGm - F7v circuit"), V6A, and PG/PP. F7 has no connections with F1.

**Ventral premotor cortex (F4 and F5)** F4 receives cingulate input from area 24c and 24d, parietal input from area VIP (ventral intraparietal area, part of areas 5 and 7) ("VIP-F4 circuit" Colby et al., 1993; Duhamel et al., 1997a,b), as well as from PEip, and SII. F4 is more strongly connected with F3 than with F6. F5 receives cingulate input from area 24c, prefrontal input from 46v, and parietal input from PF/PFG (rostral part of the inferior parietal lobule) and SII (Godschalk et al., 1984; Matelli et al., 1986). Subarea F5ab (F5 of the arcuate bank, F5 bank) also receives input from area AIP (anterior intraparietal area, part of area 7, Taira et al., 1990; Sakata et al., 1995; Luppino et al., 1999, "AIP-F5ab circuit"). In contrast, subarea F5c (F5 of the cortical convexity, F5 convexity) receives main parietal input from PF ("PF-F5c circuit"). F5 is more strongly connected with F6 than with F3. Only F5ab projects to F1 (Matelli et al., 1986; Luppino et al., 1993).

## Chapter 4

# Physiology

Motor and sensory responses coexist in the premotor cortex. The *Premotor Theory of Attention* as introduced by Rizzolatti (1987b) was the first concept that tried to make sense of the observation that premotor neurons respond in the absence of motor behavior, and signaled the beginning of a decade-long research project in the macaque. Far from being homogeneously responsive, neuronal activation depends on a variety of behavioral parameters such as moving limb, movement type, cue or target modality, cue or target position, task instruction, movement sequence, and temporal step from instruction to execution. The variability and profile of neuronal behavior suggests that premotor neurons represent bodily, environmental and cognitive or plan-related parameters on different abstract and concrete levels. A further characteristic is that neurons with more or less specialization co-exist within one cytoarchitectonic area.

### 4.1 Stimulation and recording techniques

The most important methods for investigating cortical function are electrical stimulation and single cell recording. Premotor efferents, especially their somatotopical organization, have been investigated both by stimulation of the resting monkey and by cell recording in the passively moved or behaving monkey. Premotor afferents in turn have been analyzed by cell recording during sensory stimulation in the awake, passively attending as well as anesthetized monkey. For all protocols, a recording chamber is embedded into an acrylic, which in turn is mounted via screws on the sheer skull bone and covers the region of interest. Following recovery from this first surgery, the recording chamber is opened in a second surgery and holes are drilled through the skull (or entire parts of the skull are removed) to expose the dura. After isolation of a cell, it is tested with the standard battery of stimuli or movements. Stimulation and recording sessions using one animal are

performed for several weeks, each often lasting one entire day. Both methods are often combined with a subsequent histological investigation of the corresponding tissue.

**Intracortical microstimulation** The first study using electrical microstimulation was conducted by Fritsch and Hitzig (1870) who investigated the somatotopy in the dog's motor cortex. While these very early studies used large electrodes touching the pial surface of the cortex, Asanuma and Rosen (1972) developed the technique of intracortical microstimulation (ICMS) in which micro-electrodes are advanced directly into the cortex. Today's standard protocols use brief trains ( $< 20$  ms) of biphasic electrical pulses to evoke muscle twitches (Tehovnik, 1996). In investigating motor functions, however, longer stimulus trains of several 100 ms have been recently re-introduced to evoke complex (synergetic) responses (Graziano et al., 2002b). Graziano and colleagues (2002b) thus return to early stimulation parameters with intense and prolonged signals inducing overt movement rather than flicks or twitches evoked by modern intracortical microstimulation. The authors argue that such long durations correspond to the natural, i.e. behaviorally relevant, time scale, evoking behaviors that would last just as long as without stimulation. For instance, a 3s stimulation of the orofacial motor cortex elicited rhythmic chewing (Huang et al., 1989), and a 400ms stimulation of the superior colliculus triggered gaze shifts (Freedman et al., 1996)). Whereas other brain regions, e.g. the rat hypothalamus, have been investigated with stimulations in the seconds to minutes range, for the motor system it is still a matter of debate whether transsynaptic spread of long (and possibly also the short Jankowska et al., 1975) electrical stimulations through the adjacent network (e.g. spinal interneurons) is a to-be-avoided artifact or a necessary part of cortical function in a network (Graziano et al., 2002a). A second matter of debate concerns the intensity of stimulation. Asanuma and Arnold (1975) argued that stimulation with currents above  $60 \mu A$  would damage the cortex (leading to a restriction of considered parameters in several following studies), whereas other laboratories have stimulated successfully with intensities up to  $100 \mu A$  and more.

**Single cell recording** Tactile, visual, and auditory receptive fields and well as motor efferents can be studied by single cell recording. For the former, recordings are taken either from the awake, fixed monkey (Rodman, 1991) or under anesthesia (Desimone & Gross, 1979). For motor fields, the monkey is either allowed to move certain limbs freely, or it is provoked or trained to perform certain movements while the rest of its body is fixed; passive movements of the monkeys' limbs are performed under anesthesia.

## 4.2 Efferents

Until recently, one of the main assumptions concerning the motor system was its hierarchical organization: Premotor cortex projects to and controls the primary motor cortex, which in turn projects to and controls the spinal cord. However, most of the motor areas that have been discovered in the last decades send direct projections either to the spinal cord or to the brain stem (Murray & Coulter, 1981; Dum & Strick, 1991, 1996; Maier et al., 2002). This finding shows that, although primary motor cortex may still be the primary source of corticomotoneuronal neurons that have direct access to motoneurons (Porter, 1987), there is no single motor area that passes the cortical input to the spinal cord, and hence the term or at least the definition of a *primary motor cortex* is questionable. Likewise, somatotopic organization has been a hallmark of the primary motor cortex (Penfield & Rasmussen, 1950; Woolsey et al., 1952), but it can no longer be a criterion to distinguish primary from premotor cortex. First, somatotopic organization in primary motor cortex is constrained by several factors such as the convergence and divergence of primary motor output. Second, somatotopic representations are not restricted to the primary motor cortex, but exist throughout the entire premotor cortex (see chapter 4.2.2).

### 4.2.1 General properties

Excitability to electrical stimulation differs considerably between motor areas; it is particularly high in F1 and F3 and lowest in F6 and F7. Excitability of other motor regions lies somewhere between these two extremes<sup>1</sup>. For instance, forelimb movements could be triggered in the owl monkey using about 10  $\mu A$  in primary motor cortex, 36  $\mu A$  in PMv (F4, F5), and 60  $\mu A$  in caudal PMd (F2), respectively (Preuss et al., 1996). Overall, thresholds are higher for the ventral than for the dorsal fields, and higher for the rostral than the caudal fields. This rostro-caudal trend applies also within F1, i.e., within one and the same cytoarchitectonically defined area, and may also be true for other motor areas. Independent of the intensity of stimulation, the amount of excitable neurons differs in considered areas. This gradient parallels excitability thresholds, with e.g. 99% excitable neurons in F1, 80% in F3 and 20% in F6 (standard ICMS protocols). Excitability is generally consistent with projections of considered areas to the spinal cord (or brain stem) and to the primary motor cortex. For instance, the fact that F6 is poorly excitable is consistent with the absence of direct connections to F1 (Luppino et al., 1990). Two parameters of triggered movements appear to co-vary with excitability: speed

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<sup>1</sup>However, longer stimulus train durations, higher stimulation intensities, or application during natural movements increase excitability of investigated areas (see e.g. Luppino et al., 1991).

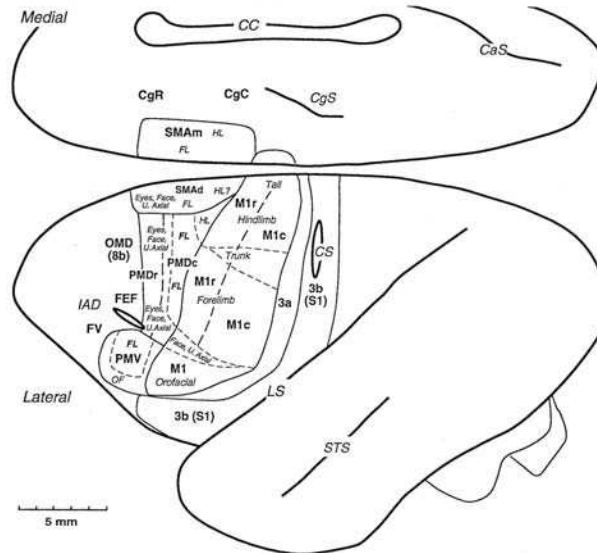


Figure 4.1: Location and somatotopic organization of cortical motor areas in owl monkeys. Stimulation of the primary motor cortex (MI) the dorsal and ventral premotor areas (PMd, PMv) and the supplementary motor area (SMA) produced somatic movements. Eye movements could be elicited from SMA and PMd as well as from the frontal eye field proper (FEF), OMD (dorsal oculomotor area), and FV (frontal ventral area) (Preuss et al., 1996).

and complexity<sup>2</sup>. Highly excitable areas show fast and simple movements, while less excitable areas show rather slow and complex movements. For instance, the percentage of complex movements from all elicited movements increases from F1 (5%) over F3 (30%) to F6 (40%), which shows characteristically slow and global movements that resemble natural movements (Luppino et al., 1991).

### 4.2.2 Somatotopy

Stimulation studies have shown that multiple somatotopical maps exist in the motor system. A broad somatotopic representation has been repeatedly confirmed for MI, with hindlimb movements mediodorsally, and trunk, forelimb, and orofa-

<sup>2</sup>The terms *simple* and *complex* are not unequivocally defined. Mostly, simple movements are conceived of as being restricted to a single joint or the digits of one extremity, whereas complex movements are those with displacements of more than two articulations or of noncontiguous articulations or body parts, such as shoulder and wrist. Contiguous movements are those where displacements occur at two adjacent joints. Note that complexity in motor tasks, especially in human studies, is defined differently (see e.g. Picard & Strick, 1996).

cial movements represented at successively more lateral and ventral levels (Gould et al., 1986; Stepniewska et al., 1993; Preuss et al., 1996). The somatotopical maps of the lateral premotor cortex lie in rough correspondence, each with more or less overlap. There is a forelimb and hindlimb representation in PMd, and an orofacial and forelimb representation within PMv; overlap is higher within PMv than within PMd (Hast et al., 1974; Kurata et al., 1985; Kurata & Tanji, 1986; Gentilucci et al., 1988; Rizzolatti et al., 1988; Kurata, 1989; He et al., 1993; Hepp-Reymond et al., 1994; Preuss et al., 1996; Graziano & Gandhi, 2000; Yoshino et al., 2000). Lateral premotor cortex' projections to F1 are hence generally also somatotopically organized (Matsumura & Kubota, 1979; Muakkassa & Strick, 1979; Godschalk et al., 1984; Matelli et al., 1986; Dum & Strick, 1991; Luppino et al., 1993), respecting the mapping of the primary motor cortex by horizontally organized projections (Figure 4.3). It is controversial whether forelimb representation of PMd and PMv are contiguous (Godschalk et al., 1995) or rather separated by an upper axial and face representation that might be buried within the arcuate spur and arcuate sulcus (Preuss et al., 1996, see Figure 4.1). Furthermore, whereas forelimb and hindlimb representations are largely separated, proximal and distal movements, at least of the hindlimb, show a greater overlap (Hatanaka et al., 2001, see Figure 4.2). Authors generally agree that within PMv, both proximal and distal forelimb movements are represented that again respect the typical somatotopical arrangement. Thus, F4 neurons are related to proximal forelimb movements, whereas F5 neurons are rather related to distal ones (Gentilucci et al., 1988; Rizzolatti et al., 1988; Luppino et al., 1999, cf. Figure 4.4). Note that due to different views on the border between PMd and PMv (see also chapter 5.2), others have reported proximal forelimb movements (involving the shoulder and/or elbow) to be more frequently triggered from PMd than from PMv, whereas the opposite is true for distal forelimb movements (involving the wrist and digits Preuss et al., 1996). In contrast to findings that base on tracer methods and that indicate both distal hindlimb (digits and ankle) and proximal hindlimb (knee and hip) but only proximal forelimb movements to be represented in PMd (Tokuno & Tanji, 1993), stimulation revealed also both distal and proximal forelimb movements to be triggered from PMd (F2vr)(Raos et al., 2003). Area F3 (SMA) contains a body map of face, forelimb, and hindlimb in an overlapping rostrocaudal sequence (Macpherson et al., 1982; Mitz & Wise, 1987; Luppino et al., 1991; He et al., 1995; Tanji & Shima, 1996). A similarly arranged map exists in area 24d, and a less excitable and less organized one in area 24c (Luppino et al., 1991). In contrast, stimulation of area F7 (SEF) and that of the FEF elicits eye movements only (Schlag & Schlag-Rey, 1987; Huerta & Kaas, 1990; Luppino et al., 1991), and area F6 contains only a representation of the arm (Luppino et al., 1991).



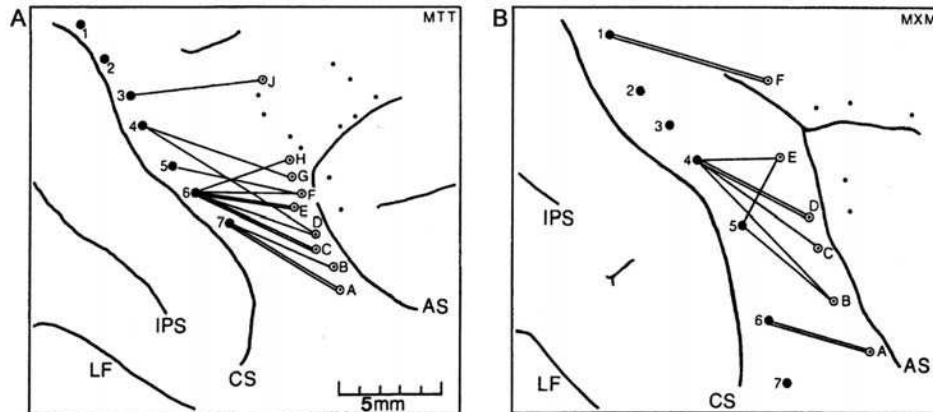


Figure 4.3: *Topographic distribution of projections between right lateral premotor and primary motor cortex shown in two monkeys (A and B). Neurons in the post-arcuate region can only be activated antidromically by electrical stimulation within restricted regions of the primary motor cortex. Abbreviations: AS arcuate sulcus, CS central sulcus, IPS intraparietal sulcus, LF lateral fissure (Godschalk et al., 1984).*

cal area, a compromise might exist between more frequently used combinations, those involving for instance the thumb, which are represented at more locations than less frequently used ones, for instance those involving the toes. Such a distributed organization also enhances the system's robustness in case of lesions. Closely related to this second issue, finally, somatotopical segregations generally parallel the biomechanical independence of different body parts. Thus, the thumb can be represented quite independently from the lips, but not from the fingers or the wrist. Recent findings from electrical microstimulation have extended the notion of a somatotopical movement representation in a challenging way (Graziano et al., 2002c). Data indicate that the lateral premotor cortex contains a representation of complex, behaviorally meaningful postures of the arm in space. This arm *posture map* is supposedly embedded between other posture maps, one ventral map of face and mouth postures, and one dorsomedial map of leg and foot postures. In contrast to these latter maps, however, only the arm postures are suggested to be arranged in a topographic manner.



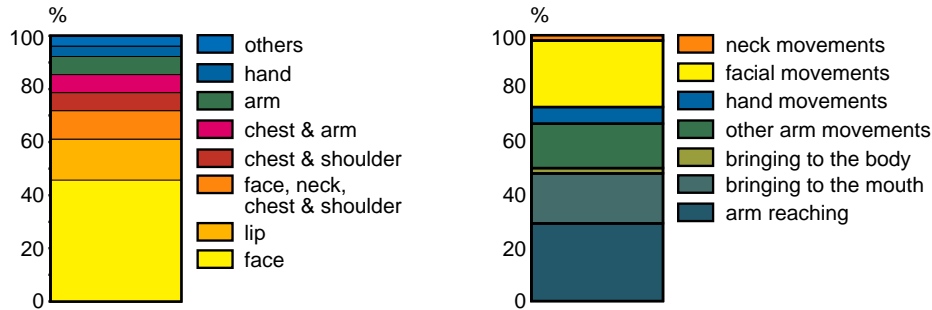


Figure 4.4: *Premotor F4 neurons: Tactile receptive fields (left) and movement representation (right) (Gentilucci et al., 1988).*

### 4.3 Afferents

In the last decades of monkey research it has become clear that neurons located in a frontal region classically considered as motor respond to sensory stimulation, in addition to their motor discharge. Kubota and Hamada (1978) were the first to report visual responses of neurons around the genu of the arcuate sulcus. Today it is known that there are motor, unimodal visual and somatosensory, bimodal visuo-somatosensory, and trimodal visuo-audio-somatosensory neurons in the monkey premotor cortex (Rizzolatti et al., 1981b,a; Gentilucci et al., 1988; Fogassi et al., 1996; Graziano et al., 1997a, 1999) (for review see also Fadiga et al., 2000). For instance in a study on area F4, 87% of neurons responded to sensory stimuli, with tactile (30%), visual (14%), and bimodal visuotactile neurons (56%) (Fogassi et al., 1996). Among distal (grasping) neurons in area F5, 42% responded to tactile and 17% to visual stimuli (though the study leaves open whether these two classes overlap). Visual responses of area F5 are more complex than those reported for F4, as will be discussed below (see chapter 4.4.3).

Responses to visual, tactile, and auditory stimuli are even found in monkeys that are trained not to react to the stimuli and in anesthetized animals. Since sensory responses are independent of the task and even consciousness, it can be ruled out that they simply represent motor preparatory responses. Note that a neglect of both tactile and visual stimuli of the contralateral personal and peripersonal space is observed after lesion (Rizzolatti et al., 1983) or reversible inactivation (Schieber & Poliakov, 1998; Fogassi et al., 2001) of area F4 and F5. The fact that sensory responses are strictly bound to stimulation and that they are highly constant across trials suggests that they are truly sensory. However, since receptive fields are restricted to the peripersonal space and typically three-dimensional, an alternative interpretation holds that sensory responses reflect an automatically triggered po-

tential action that map space in terms of a *motor act vocabulary* of different limbs (Fadiga et al., 2000, see chapter 4.4). Premotor neurons with sensory properties are more frequently found in the rostral premotor cortex, and those with motor properties more frequently in the caudal (Johnson et al., 1996; Shen & Alexander, 1997a; Wise et al., 1997). This finding parallels connectivity patterns, since direct projections exist between rostral premotor and prefrontal areas on the one hand and between caudal premotor cortex and MI respectively the spinal cord on the other (Dum & Strick, 1991; Ghosh & Gattera, 1995; Marconi et al., 2001). Both properties indicate that rostral premotor fields may be rather seen as functionally belonging to the prefrontal cortex, whereas caudal premotor cortex is rather conceived of as a true motor area that is primarily involved in movement execution. However, the exact distribution of sensory responsive neurons within motor areas is not yet settled, partly because a systematic mapping within the entire precentral area in awake animals is technically problematic. Probably only little visual information reaches F1 (Kurata & Tanji, 1986; Wannier et al., 1989). For the mesial premotor fields, neuronal responses to visual stimuli prevail in F6, but somatosensory responses are rare; the opposite is true in F3 (Matsuzaka et al., 1992). Visuotactile neurons have been identified both in PMv and in PMd, though PMd has not yet been tested thoroughly. Spatially organized visual peripersonal receptive fields around tactile ones are especially typical for F4. Auditory responses are much rarer than visual or tactile responses. The only study on sensory responses that mapped the entire lateral premotor belt in anesthetized monkeys (Graziano & Gandhi, 2000, Figure 4.5) reported neurons along the entire premotor cortex to respond to the tactile stimulation of the leg, hand, arm, face, and mouth. Bimodal neurons for face, hand, and arm representations were found around the arcuate spur; within the same area ("Polysensory Zone", PZ), trimodal neurons were found in two of five animals. Rostral PMd (supposedly F7) was the only area to be generally unresponsive in the anesthetized animals.

#### 4.4 Sensorimotor transformation

What is the function of sensory responsive neurons in the premotor cortex? An important hint comes from the finding that receptive fields are typically registered to the body part whose motion is represented by the same neuron. In case of bi- and trimodal neurons, receptive fields are largely co-registered to one another. A peculiar subtype of visual F4 neurons is even retinocentric, not retinotopic, i.e. their receptive field maintains the same position on the retina regardless of the eye position (Boussaoud et al., 1993; Graziano et al., 1994; Fogassi et al., 1996). Such a representation of stimuli in body-part centered coordinates appear to provide a general solution to the problem of sensorimotor integration. PM contains a variety

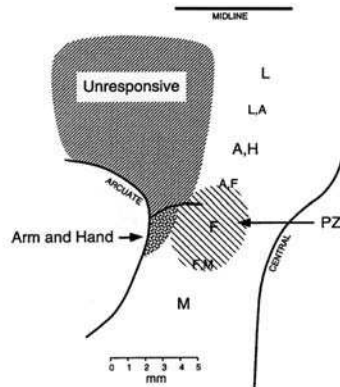


Figure 4.5: *Spatial organization of tactile, visual and auditory responses in the precentral gyrus, summarized from five experimental monkeys. Letters refer to the somatotopical organization of tactile responses. The area in which neurons were found to respond to tactile, visual and also auditory stimulation is labeled PZ (polysensory zone). Abbreviations: L leg, A arm, H hand, F face, M mouth (Graziano and Gandhi, 2000).*

of neurons that code environmental features in a very specific way, such as canonical, mirror, and space coding neurons. Together, they are suggested to provide a tool for the spatial and higher order representation of actions. Their role in sensorimotor transformation is typically exemplified by PMv neurons that translate the visual features of objects into a potential grasping action, but this function may as well be generalized for all types of goal-directed actions. As outlined above, sensory responses of PMv neurons are taken to address a motor or action "vocabulary" that is selected in different ways for different purposes. Simplified, the F4 vocabulary codes reaching movements related to object spatial location, and the F5 vocabulary grasping movements related to space-independent object properties. Furthermore, F5ab and F5c differ with regard to the way in which their action vocabularies are selected, the former being responsive to object presentation, the latter to action presentation. As far as premotor neurons have been investigated, it is characteristic that the specific neuronal tuning (for grasping, for holding, for action observation and so on) is additionally modulated by the phase in which neurons respond in the course of an action or attentional process. That is, tuning of premotor neurons is multidimensional. Conceptually, two types of sensorimotor mapping have been distinguished to stress fundamentally different requirements: *standard* and *nonstandard sensorimotor mapping* (Wise et al., 1996). The former refers to spatially congruent guidance of the eyes, limbs and body toward targets

in visual space. In contrast, the latter occurs in situations in which the system must reject the commonplace correspondences among visuospatial stimuli, gaze, attention and reaching movements. This is required whenever we gaze in one direction while reaching in another or in conditional motor tasks when the color of an object instructs a movement elsewhere in space, i.e., whenever there is an arbitrary correspondence between the sensory situation and the motor act. A crucial assumption is that premotor cortex underlies not only standard mapping, but also nonstandard mapping, and therewith the behavioral flexibility that such a function allows.

#### 4.4.1 Multiple frontoparietal loops

Motor and parietal areas are reciprocally connected in multiple highly specialized, largely segregated, parallel working circuits (Rizzolatti et al., 1998). Each premotor field receives afferents from a set of different parietal areas, but typically input is strongest from one parietal area to one premotor area. Areas linked by predominant connections in such a circuit are suggested to share common functional properties, dedicated to a specific sensorimotor transformation. Thus, like premotor areas, the posterior parietal lobule contains a multiplicity of arm, leg and face representations, and both its inferior and superior compartments (IPL and SPL) receive visual and tactile inputs. In particular, visual information is mainly processed in the posterior IPL and SPL, whereas tactile information processing takes place in the anterior SPL; visual and tactile information is integrated in anterior IPL (Rizzolatti et al., 1997; Wise et al., 1997). According to a recent computational model (Fagg & Arbib, 1998) parietal areas provide multiple pragmatic descriptions of three-dimensional stimuli and thereby propose several action possibilities to the corresponding premotor field. This in turn selects the appropriate action on the basis of motivational and other contextual information. Notably, the product of such a sensorimotor transformation is not necessarily a motor action, but rather a *potential action* or *motor idea* (Fadiga et al., 2000). The transformation of this potential action engages additional areas, most probably area F6 (the preSMA), which talks in turn with lateral prefrontal (area 46) and frontomedian areas (area 24c). Area F6 may relay results from planning and memory functions to the premotor-parietal circuits, thereby releasing a potential action for overt performance (Figure 4.6).

There are a number of recent elaborated overviews on the organization and function of the premotor-parietal loops (e.g. Geyer et al., 2000a) whose suggested functions will therefore be only shortly outlined in the following. Data provide evidence for three dorsal and three ventral premotor-parietal loops. The F2vr-MIP/V6A loop is involved in the transformation of tactile and visual information for the control of the transport phase of the hand toward the target;

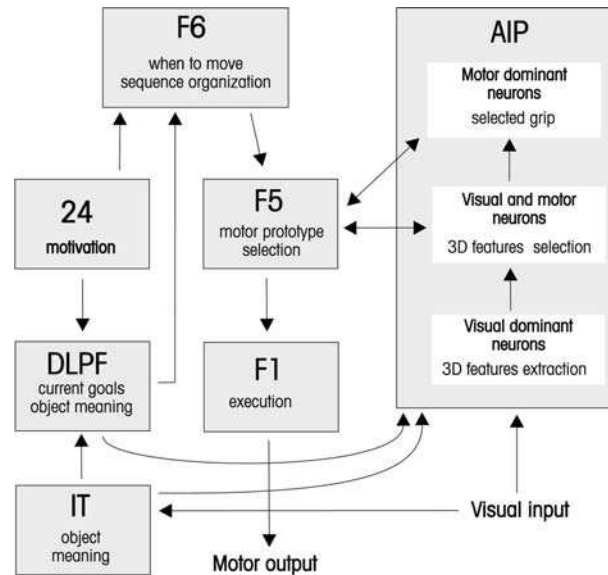


Figure 4.6: Schematic model of sensorimotor transformation in grasping as proposed by Fagg and Arbib, 1998.

F2vr contains leg and arm efferents and proprioceptive and visual neurons. The F2dimple-PEip/PEc loop is engaged in planning and controlling arm and leg movements on the basis of tactile information. The third dorsal loop, F7-FEF-DLPFC-PGm/V6A, codes object locations in space for orienting and coordinating arm-body movements; premotor areas have oculomotor efferents and visual neurons. The ventral F4-VIP loop is involved in encoding peripersonal space according to a body part-centered reference frame and in the transformation of object location into appropriate movement towards them; F4 contains arm, neck, face, and mouth efferents, and has tactile and visuo-tactile (bimodal) neurons. The F5ab-AIP loop underlies the creation of a pragmatic representation of the object, in which intrinsic properties of the object like size, shape and orientation are coded in order to select the most appropriate way to grasp it; F5ab has hand and mouth efferents, and contains tactile, visual, visuo-tactile and visuo-audio-tactile (trimodal) neurons. F5ab contains a specific neuron type, the *canonical neurons* (see chapter 4.4.3). Having the same efferent and afferent profile, the other sub-area of F5 builds the F5c-PF loop which is suggested to match observation with execution of a motor action, and hence to underlie the understanding of observed actions. The specific type of neurons that are engaged in this high-level coding are the *mirror neurons*.

### 4.4.2 Spatially tuned neurons

Sensorimotor coordinate transformations are required because sensory information is coded in the coordinates of the sensory epithelia (e.g. retina, skin) (extrinsic reference frame) and must be transformed to the coordinates of muscles for movement (intrinsic reference frame) (Soechting & Flanders, 1992). Neurons underlying coordinate transformations expose a characteristic behavior: Their activity is a function of both the extrinsic and the intrinsic reference frame. E.g. neurons in parietal area 7a code both the position of a target on the retina and the position of the eyes in the orbit, suggesting that these cells underlie the transformation of the target location in a retinotopic coordinate frame to the target location in a head-centered coordinate frame (Andersen et al., 1985). The transformation is supposed to be performed with progressive shifts from extrinsic to intrinsic reference in a serial or hierarchical manner. Contrary to former views it is now widely accepted that brain correlates underlying sensorimotor transformation are fairly distributed. Already on the parietal level, different reference frames exist for incoming stimuli, and the same appears to be true for the premotor areas. Spatially tuned premotor neurons have been identified throughout the premotor cortex, including gaze-dependent and gaze-independent neurons in PMv<sup>4</sup> (Gentilucci et al., 1983; Matelli et al., 1986; Rizzolatti et al., 1988; Fogassi et al., 1992; Boussaoud & Wise, 1993a; Graziano et al., 1994; Sakata et al., 1995; Freedman et al., 1996; Rizzolatti et al., 1996; Mushiake et al., 1997; Graziano & Gross, 1998), PMd (probably F2vr) (Caminiti et al., 1991; Fu et al., 1993; Crammond & Kalaska, 1994; Shen & Alexander, 1997a; Boussaoud et al., 1998) and both SMA and primary motor cortex (Alexander & Crutcher, 1990a,b; Crutcher & Alexander, 1990; Matsuzaka et al., 1992; Shen & Alexander, 1997b). Considered neurons code (a) the direction of a planned or performed limb movement, (b) the amplitude of a planned or performed limb movement, (c) the target location independent of limb trajectory, (d) the cue location independent of target location and movement direction<sup>5</sup>, and (e) the stimulus location independent of movement intention or task. In F4, bimodal neurons were even found to exhibit object permanence, i.e. they encoded the presence (location) of an object within their receptive field that was no longer visible (Graziano et al., 1997b).

The exact functional interpretation of space coding remains a matter of debate, especially for spatially tuned neurons that are independent of gaze. A somewhat unique but nonetheless suggestive hypothesis is that spatially tuned PMd neurons function in the suppression of inappropriate movements (Sawaguchi et al.,

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<sup>4</sup>This refers to subarea F4 in most studies, though recent experiments have identified some spatially tuned F5 neurons (e.g. Fogassi et al., 2001).

<sup>5</sup>Lebedev and Wise (2001) report 20% of gaze-independent spatially tuned neurons to be only modulated by cue position, hence reflecting "selective spatial attention".

1996; Praamstra et al., 1999). However, the prevailing view states the opposite: Spatially tuned visual neurons extend the personal space into the peripersonal (possibly also the far) space, and hence provide a subclass of neurons that guide voluntary movements. This is supported for instance by the finding that in F4, visual receptive fields are typically restricted to the reaching distance (peripersonal space) and most of them code space in somatocentric coordinates anchored to the head and the arms, i.e. gaze-independent. It is still controversial whether different space sectors are coded in different premotor areas (Rizzolatti et al., 1983; Iacoboni et al., 1997). In particular, far space coding and oculomotor control has been attributed to PMd-parietal circles, whereas near space (i.e., personal (cutaneous) and peripersonal space) coding and limb movement control is attributed to PMv-parietal circles. In support of this view, parietal areas that project to FEF (area 7a) and SEF (LIP) code space in retinotopic coordinates, whereas areas that project to area F4 (VIP and area 7b) code space in somatocentered coordinates.

Directional tuning exists not only in premotor, but also in primary motor cortex. For instance, Kakei and colleagues (Kakei et al., 2003) investigated step-tracking movements of the wrist in monkeys and found directional tuning in about half of the task-related neurons in both PMv and MI. This study employed a task developed to dissociate between three major variables of wrist movement: muscle activity, direction of movement at the wrist joint, and direction of movement in space (Kakei et al., 1999). Authors found that direction-dependent neurons dominated in the PMv as compared to joint-direction-dependent neurons (85% versus 12%). In contrast, primary motor cortex showed about the same amount of direction-dependent and joint-direction-dependent neurons, and in addition also about the same amount of muscle-dependent neurons (24%, 37%, and 39%) which were absent in PMv. Authors proposed that these different neurons in the monkey motor areas reflect different steps in the sensorimotor transformation, with joint-direction-dependent neurons being an intermediate step between extrinsic (direction-dependent) and intrinsic (muscle-dependent) reference frames of action coding<sup>6</sup>. The prevalence of direction-dependent neurons in PMv, together with the finding that their activity precedes those in MI (Kakei et al., 2001), supports the higher role and/or earlier engagement of premotor as compared to primary motor areas in goal-directed action, and thus a distributed sensorimotor transformation. This view is further supported by a study that uses a fairly sophisticated mathematical approach in analyzing single neuron behavior in the primary motor cortex (Zhang et al., 1997). Findings demonstrate that even within primary motor cortex, neuronal activity is differently modulated during the course of a stimulus-response

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<sup>6</sup>Note that "extrinsic" as used by Kakei and colleagues does not necessarily mean "retinocentric", but could also be somatocentered. The hybrid spatially-and-muscle-tuned neurons resemble the subtype of somatocentered neurons in F4 reported by Fogassi and co-workers (1996) that are modulated by eye-position.

task. In the beginning, neuronal activity is a function of the stimulus, then one of the stimulus-response-mapping rule as well as the trial-specific stimulus-response association, and finally it depends on the behavioral response.

#### 4.4.3 Canonical and mirror neurons

Although neurons for tearing, holding, manipulating and other movements exist within F5, most F5 neurons are grasping neurons that are engaged in different specific phases and types of grasping. Some grasping neurons are unspecific for limb and grip type, i.e., grasping a target with the right or left hand or the mouth can engage the same neuron (Rizzolatti et al., 1987a). Most of the grasping neurons in turn are also activated by the mere presentation of visual objects. Activation of these so-called canonical neurons (found in area F5ab Murata et al., 1997; Rizzolatti & Fadiga, 1998, Figure 4.7) is highly reliable, temporally locked to the stimulus presentation, and observed even when grasping movements are explicitly excluded - characteristics that are usually considered good evidence in favor of the true sensorial nature of a response and excluding an intentional interpretation at the same time. In considered studies more than half of the canonical neurons were found to be selective to one or a few specific objects (as far as they were tested). Interestingly, this object-selectivity frequently matches selectivity for a corresponding grip type, suggesting that one and the same neuron codes an object description in visual and motor terms. Responses of canonical neurons to object presentation are thus taken to be neither visual nor intentional but to represent the description of the presented object in motor terms, i.e. the pragmatic physical properties of objects. Every time an object is presented, such neurons automatically translate its visual features into a potential motor action (Murata et al., 1997; Fadiga et al., 2000).

A second important type of visuomotor F5 neuron, found especially in area F5c in the cortical convexity, are the mirror neurons (di Pellegrino et al., 1992; Gallese et al., 1996, Figure 4.7). Like for canonical neurons, both an action-selectivity and a (stricter or broader) *congruence* between perceptual selectivity and action-selectivity are also typical for mirror neurons. Unlike canonical neurons, however, mirror neurons do not respond to the mere presentation of objects, but to the interaction of others (animal or human) hand or mouth with a given object. Whereas mirror neurons were first discovered for manual object-directed actions, one-third of mouth motor neurons were recently also reported to discharge when the monkey observes another individual performing mouth actions (Ferrari et al., 2003). Since this study found not only mirror neurons related to ingestive functions, but also those which were most responsive to communicative mouth gestures, authors take their findings to confirm the homology assumption on area F5 and human BA 44 (see chapter 5.2). The concept of mirror neurons is



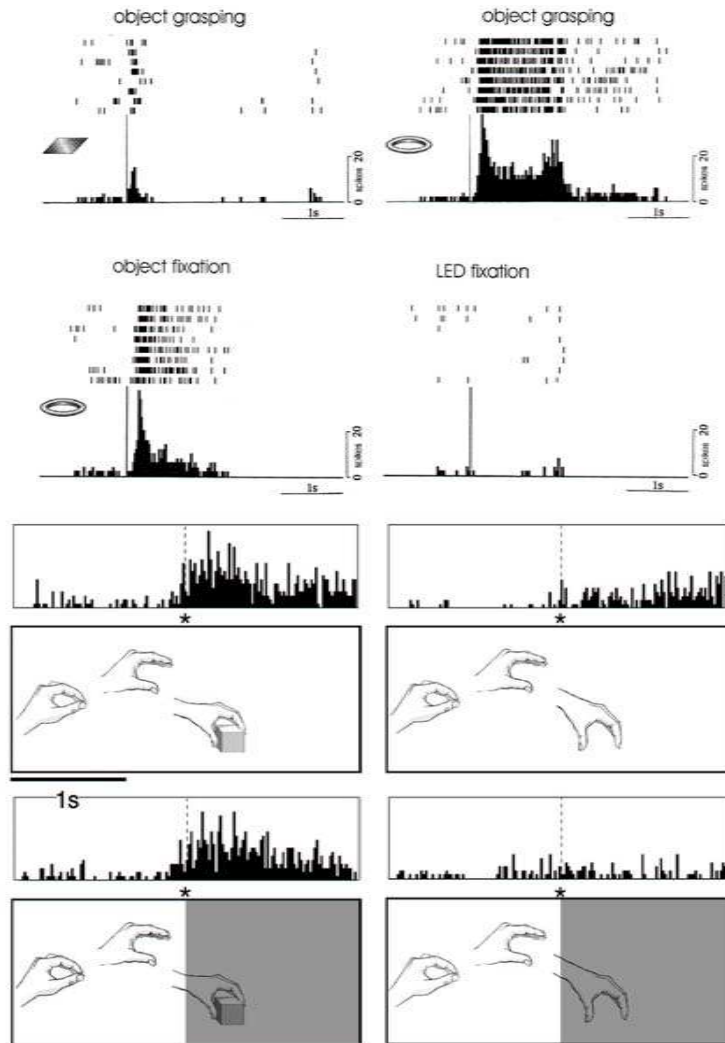


Figure 4.7: Upper panels show a canonical neuron that is selective for the grasping and the perception of a ring (Rizzolatti & Luppino, 2001). Lower panels show a mirror neuron responding to action observation in full vision and in hidden condition but not in mimed conditions (Umiltà et al., 2001).

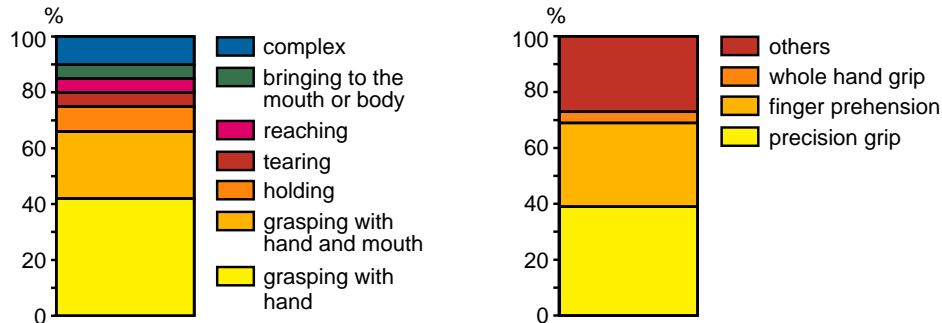


Figure 4.8: *Premotor F5 neurons: Movement representation (left) and subtypes of grasping neurons (right) (Rizzolatti et al., 1988).*

not restricted to vision, but has been extended by audiovisual mirror neurons that code actions independently of whether these actions are performed, heard, or seen (Kohler et al., 2002). Higher order representations of actions in area F5c are further implicated by reversible inactivation studies that confirm that only area F5ab, but not area F5c, contributes to fine-tuned object grasping (Fogassi et al., 2001).

#### 4.4.4 Phase-tuned neurons I: signal-, set-, movement-neurons

One of the characteristic features distinguishing premotor areas from primary motor cortex is that the former are less strictly locked onto movement onset, but rather precede movement and even respond to sensory events (Tanji et al., 1988; Crammond & Kalaska, 1996). All task-related neurons as described above are orthogonally modulated by an additional factor: the task phase in which the neuron is active (e.g. Kurata, 1989). Basically, three classes of neurons are distinguishable: *Signal-related* neurons which show a phasic discharge after instruction cue presentation, *set-related* neurons (or "delay neurons") that discharge tonically during the instructed delay period, and *movement-related* neurons that fire after the go signal, that is, in relation to the movement itself. Finally, there are premotor neurons, characterized by a combination of two or all of the three described activities (Boussaoud et al., 1998; Kakei et al., 2001, Figure 4.9). It is very interesting that, as for uni-, bi- and trimodal sensorimotor neurons, neurons show also more or less preference for one or several task phases. Sometimes *movement-related* neurons are in turn further subdivided into *premovement-related* (what is not the same as set-related) and *movement-related* neurons. Within this terminological frame, the visual, auditory, tactile, bimodal and trimodal neurons discussed above would be mostly referred to as signal-related neurons.

Set-related activity is prominent in both PMv and PMd (Kurata, 1989; di Pel-

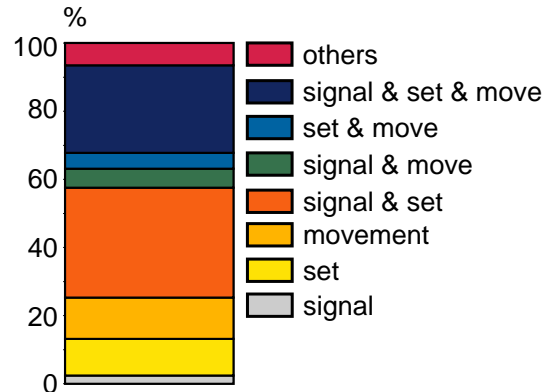


Figure 4.9: *Time-tuned neurons in the dorsal premotor cortex: percentages of reaching neurons that preferred specific task periods. Signal = task instruction (cue), set = instructed delay period between signal and movement, move = movement onset and performance (Boussaoud et al., 1998).*

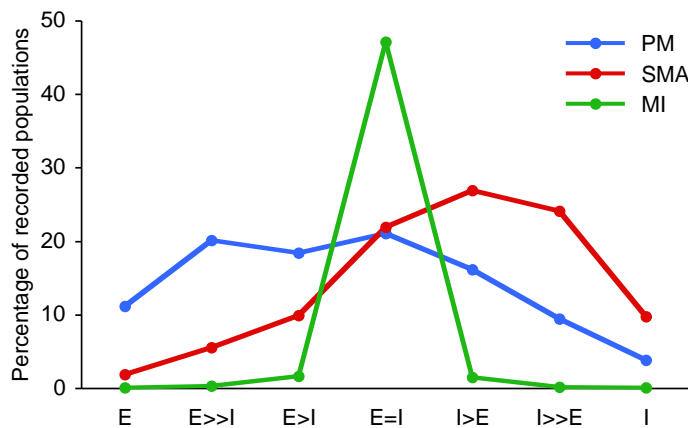


Figure 4.10: *Distribution of neurons in lateral premotor cortex (blue), SMA (red) and MI (green), classified according to their relative relations to visually (externally, E) guided versus internally (I) guided motor tasks (averaged across pre-movement, delay and movement period). Activation during complex movements under external guidance (left extreme) is more prominent in lateral premotor cortex than in SMA, whereas the opposite is true for internal guidance (right extreme). Note that this factor obviously does not influence activity in MI (Mushiakhe et al., 1991).*

legrino & Wise, 1993; Yoshino et al., 2000). However, when instructional aspects (motor significance) and sensory aspects (perceptual appearance) of the cue are manipulated independently, PMd neurons are more often modulated by the former than by the latter, whereas the opposite is true for PMv (Godschalk et al., 1985; Boussaoud & Wise, 1993a,b; di Pellegrino & Wise, 1993; Kurata, 1993; Kurata & Hoffman, 1994). Therefore in PMv, set-related activity has been proposed to reflect readiness to acquire a target in space, whereas in PMd, it rather relates to readiness to use a selected limb (Hoshi & Tanji, 2002, Figure 4.11). Accordingly, PMv rather than PMd is taken to resemble prefrontal neurons engaged in the sensory processing of visuospatial memory (for discussion, see Kurata, 1994). It has to be considered, however, that most of the studies supporting this ventral-dorsal dissociation have investigated reaching movements. As such they draw on PMd rather than on PMv due to the use of the arm (see chapter 4.2.2), and hence possibly confound limb-specificity with set-specificity. Corroborating this assumption, the majority (75.9%) of set-related PMv neurons engaged in a visually guided jaw-movement task were specialized for either opening or closing movements (Yoshino et al., 2000). It is therefore arguable whether set-related neurons are specific for the dorsal premotor cortex.

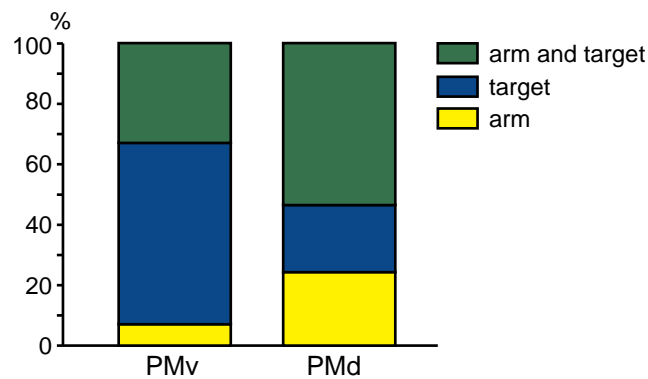


Figure 4.11: *Set-related reaching neurons in the ventral (PMv) and dorsal (PMd) premotor cortex. Activity of neurons was tuned to different amounts by two factors: the reaching limb (right or left arm) and the target position (right or left side from the body). Most task-related PMd neurons are tuned by both ("preparation for action") whereas most task-related PMv neurons are tuned by target position only ("preparation for target acquisition"; Hoshi and Tanji, 2002).*

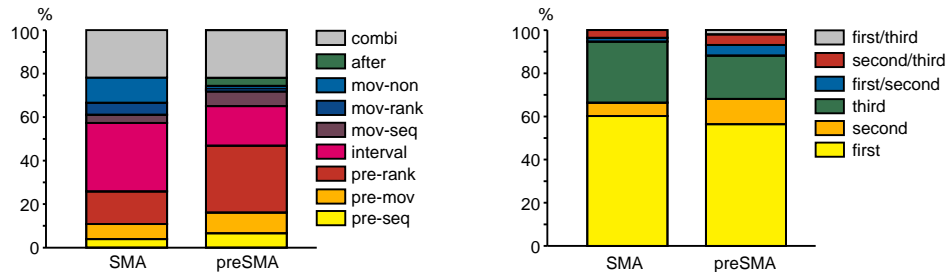


Figure 4.12: The left panel shows the distribution of neurons exhibiting relationships to various aspects of a classical turn-push-pull sequencing task. Neurons were selective for the sequence (seq), for the movement (mov), for the rank order (rank), for the interval periods (interval) or for the post-movement period (after). Moreover, selectivities referred to the preparatory period (pre-) or to the execution period itself (mov-). Some neurons were tuned to combinations of these features (combi). The right panel shows the selectivity of rank-order selective neurons to the first, second, or third preparatory period in the SMA and the preSMA, demonstrating that most of these neurons are interested in the first period (Shima and Tanji, 2000).

#### 4.4.5 Phase-tuned neurons II: sequence-neurons

Sequence-tuned neurons can be conceived of as phase-tuned neurons that are highly specialized not for single (simple) but for sequential (complex) movements. These neurons have been identified and intensively investigated within the pre-supplementary and supplementary motor area. Particularly in F6 such neurons are taken to provide a particular interplay of facilitation and inhibition that is required in motor sequences. In contrast to lateral PM sites, F6 might function in the preparation of movements and in their release when the appropriate conditions are set (Rizzolatti et al., 1990). Such a supramotor function of F6, namely the possible control of multiple lateral premotor-parietal circuits is also suggested by the fact that in contrast to all other motor areas, F6 receives only very modest input from parietal areas and has strong prefrontal inputs from area 46 and rostral cingulate cortex (see chapter 3.2, Luppino et al., 1993; Lu et al., 1994). An idea on how sequencing is realized has been recently presented by Shima and Tanji (2000). Authors provides a detailed description of different SMA and preSMA neurons underlying sequencing functions under internal (memory-based) guidance (see Figure 4.12). These findings also elaborate the assumption that preSMA and SMA are differentiated along higher- and lower-order aspects of motor control (Picard & Strick, 1996).

Even though numerous studies on premotor sequencing functions exist, it is

worth looking more closely at this study. Authors distinguish five basic types (and further subclasses) of sequencing neurons (Figures 4.13 and 4.14). These neurons fire if and only if the monkey (1) is preparing to perform a particular movement sequence, e.g. for pull-turn-push (but not for pull-push-turn) (*sequence-selective activity*); is preparing to pull (but not to push or turn), no matter whether pulling is the first, second, or the third movement in a sequence (*movement-selective preparatory activity*) (2) is preparing to perform the third (but not the first or second) movement, no matter which movement it is or which sequence is performed; or is preparing to perform either the first or the third (but not the second) movement (or arbitrary other combinations or two movement ranks), no matter which movement and sequence (*rank-order-selective preparatory activity*) (3) is preparing to perform a push movement after having completed a pull movement (but no other combination of movement types), no matter which rank or sequence (*interval-selective activity*) (4) is preparing to perform or is performing a movement (*movement-related activity*) and fires in dependence of the specific sequence (*nonselective-selective movement-related activity*), on the rank order (*rank-order-selective movement-related activity*) or on the single movement if ever (*movement-related activity*) (5) has just finished a sequence (*activity after the third movement*) Authors propose that sequential performance starts with the sequence retrieval, reflected by activity of sequence-selective neurons. In a next step, the sequence is initiated by movement-selective preparatory neurons. Interval-selective neurons subsequently provide the link to the next element in the sequence, whereas rank-order selective neurons serve to regulate the linking-element information. Neurons that are active after the last movement in a sequence may signify an end signal. Even though this model has to be confirmed by future studies, it is the most elaborate and plausible model of preSMA/SMA sequencing function to date.

An open question remains as to whether sequence-tuned neurons described for the mesial premotor cortex also exist within the lateral PM. Indirect evidence against this view can be derived from the following rationale: In the study of Shima and Tanji cited above, preparatory and interval-selective neuronal activity is absent under visual guidance, but develops gradually in parallel with the repetition of the trials and sequence learning. This result confirms prior studies on internally and externally guided sequential (i.e. complex) movements (Mushiake et al., 1991), demonstrating that under internally guided conditions, pre-movement and movement periods were reflected by enhanced neuronal activity in SMA, whereas external guidance engaged rather the lateral PM (see Figure 4.10). During the set period, this preference was still observed in SMA, whereas PM was equally activated under both types of guidance. As pointed out by the authors, the internal-external difference that tends to dissociate SMA and PM is only present in sequential, i.e., complex movements, but not in single movements.

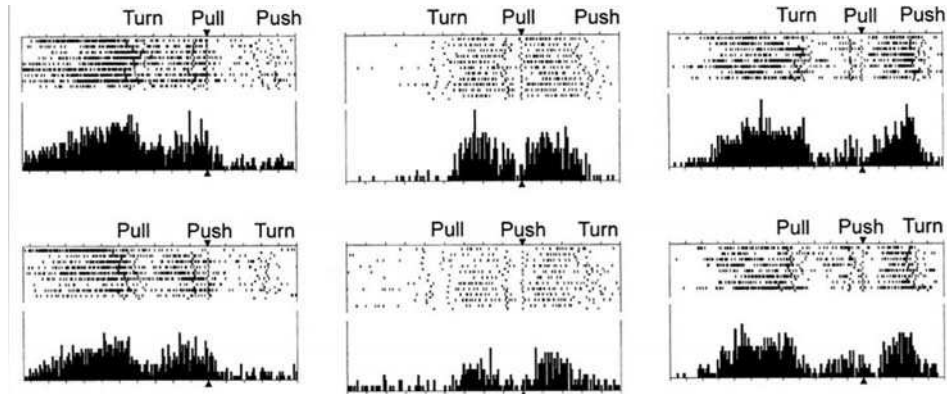


Figure 4.13: Discharge of three preSMA neurons exhibiting increased activity during more than one preparatory period (first/second, second/third and first/third type, cf. Figure 4.12 right panel). These neurons are tuned to the rank-order, independently of the type and the sequence of movements. For instance, the first neuron (left panel) responds to the first and second movement preparation, no matter whether these are "turn-pull" or "pull-push" (Shima and Tanji, 2000).

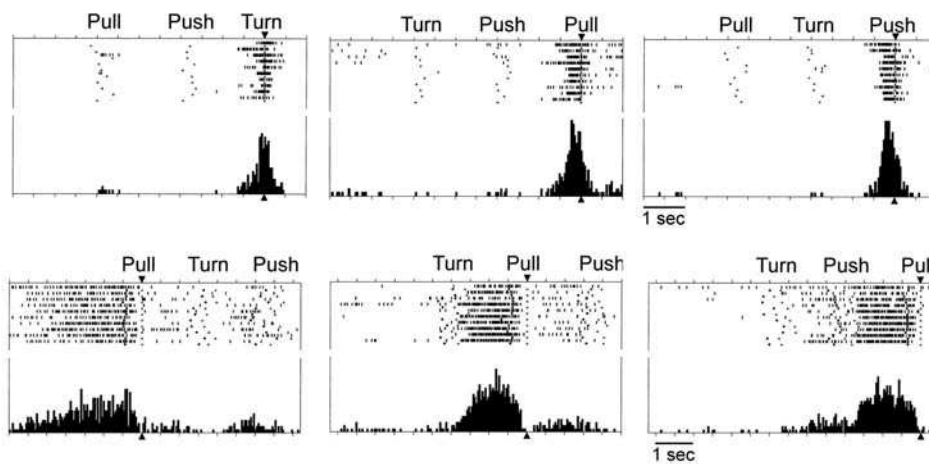


Figure 4.14: Upper panel: Discharges of a preSMA neuron whose activity increases during and before initiation of the third movement, regardless of the movement (turn, push or pull) and of the sequence. Lower panel: Discharges of a preSMA neuron whose activity increases while the animal is waiting to initiate the next movement; this neuron is selective for the preparation of a pull movement, regardless of sequence or rank-order (cf. Figures 4.12 and 4.13) (Shima and Tanji, 2000).

## **Part II**

# **Human premotor cortex**





## Chapter 5

# Structure

### 5.1 Old and new approaches

In contrast to the monkey premotor cortex, the structural parcelling of the human premotor cortex, or even its correlation to functional profiles, is largely unsettled. Although Brodmann's area "6" has been further subdivided in subsequent analyses (Sanides, 1962, Figure 5.1), these maps have never gained the same influence as Brodmann's originals. Recent approaches take the considerable inter-individual variability of structural fields into account (Amunts & Zilles, 2001). Although resulting *probabilistic* cytoarchitectonical maps exist for a number of cortical areas, an exhaustive description of the premotor cortex is not yet available. Together, quantitative cytoarchitectonic, myeloarchitectonic, transmitter receptor autoradiography as well as immunolabeling confirm a parcelling of the medial precentral areas into SMA proper and preSMA separated along the VCA line (the line passing through the anterior commissure, perpendicular to the line between both commissures (AC-PC line)) (Zilles et al., 1995, 1996; Baleyrier et al., 1997). Likewise, a structural parcelling of the primary motor cortex into an anterior area 4a and a posterior area 4p has been demonstrated (Geyer et al., 1996). Recently, Rosano and colleagues (2003) have combined cyto- and chemoarchitectonic techniques to target the human frontal eye field as defined by its activation in saccade tasks in imaging studies. As a result, the authors confirm a topographic dislocation of this area: while the monkey frontal eye field lies within the transitional cortex of the arcuate sulcus between granular (area 8) and agranular (area 6) cortex, the supposed human frontal eye field appears to be located entirely within the agranular area 6, close to the intersection of the superior precentral sulcus and the superior frontal sulcus. A structural dissociation between PMv and PMd, or between areas that could correspond to the F-fields described in the monkey, has not yet been confirmed or investigated. Of course, ethical reasons forbid the investigation of

function-structure relationships in the human motor cortex in the same way as is done in monkeys. A promising methodological development for future investigation of cortical structure, and possibly also corresponding function, is based on the effect that structural characteristics of the cortex determine changes in the intensity of its MR signal. Using specific MR protocols, cortical columns (neurons with similar functional specializations that cluster together) could be visualized at a resolution of about  $500\ \mu\text{m}$  (Damasio et al., 1991; Bendersky et al., 2003). Moreover, one has begun to combine three-dimensionally registered cytoarchitectonic maps acquired in post-mortem studies with functional imaging data acquired in living brains. First data from those approaches indicate significant correlations between architectonical and functional parcelling of the human cerebral cortex, showing how primary visual and primary motor areas contribute to sensation and movement (Geyer et al., 1996; Larsson et al., 1999; Naito et al., 1999; Bodegard et al., 2000; Ehrsson et al., 2000b; Naito et al., 2000). A further recently introduced method is the measurement of the density of transmitter receptors, the variance of which reflects both the cyto- and myeloarchitectonical as well as the functional organization of the cortex. Combining postmortem (cyto- and myeloarchitecture, quantitative in vitro receptor autoradiography) and in vivo techniques (PET receptor neuroimaging), Zilles and co-workers (2002) demonstrated that receptor distribution patterns correlate significantly with classical approaches to the architectonics and functions.

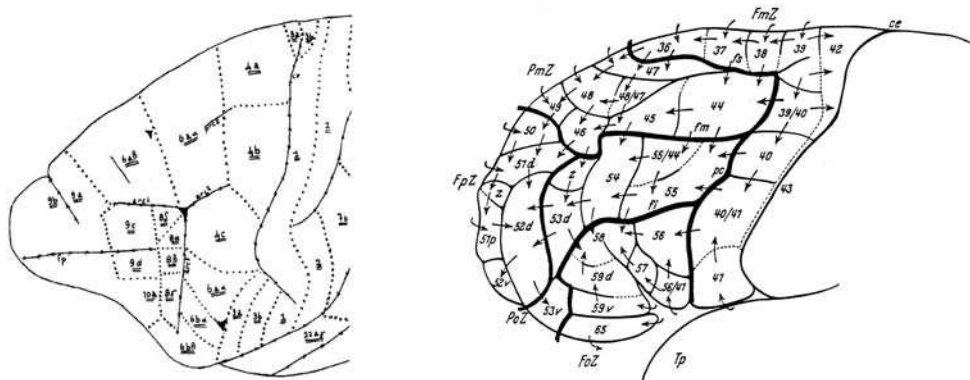


Figure 5.1: *Historical premotor parcelling as proposed in the monkey (left, Vogt and Vogt, 1919) and in humans (right, Sanides 1962).*

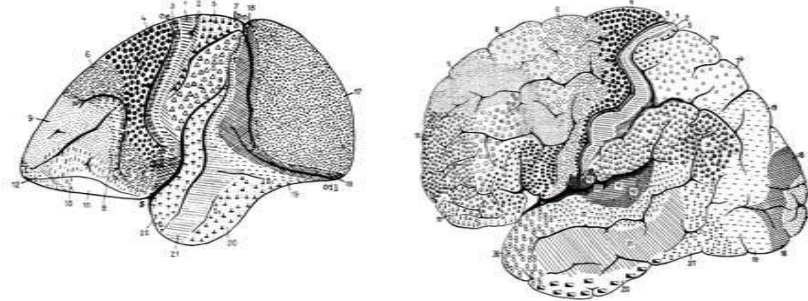


Figure 5.2: *Cytoarchitectonic maps of the monkey and the human as proposed by Brodmann (1905, 1909).*

## 5.2 Human homologies of the non-human primate

Although many cytoarchitectonic maps of the human brain have been published since the beginning of the 20th century, Brodmann's original map has remained the most influential (Brodmann, 1909, Figure 5.2). Today's labels designating cytoarchitectonically determined areas in the monkey brain have evolved without reference to the human brain and vice versa, resulting in terminological confusion. Attempts have been made to unite terminologies used for monkey and man (e.g. Petrides & Pandya, 1994), but still the most popular map for monkeys is Matelli's F-nomenclature (1985), for which a corresponding microstructural parcelling of the frontal human motor cortex has not been verified. Though some advances can be noted for the identification of cytoarchitectonical subdivisions within the medial and the dorsal premotor cortices (Zilles et al., 1995; Baleyrier et al., 1997), direct evidence is lacking concerning individual cytoarchitectonic data in conjunction with functional results, and so any potential correspondences between subsections of the human and the monkey premotor cortex are based on functional rather than on anatomical homologies (see for instance Rizzolatti et al., 2002).

**Premotor and primary motor cortex** An important basis for homology suggestions is that more than one electrically excitable body map can be identified within both the human and the monkey motor areas. An ordered movement representation in human primary motor and premotor areas (Foerster, 1936; Fried et al., 1991; Freund, 1991; Ikeda et al., 1992, 1993; Matelli & Luppino, 1997) indicates that corticospinal projections originate from both caudal area 6 $\alpha$  and area 4, as in the monkey (He et al., 1993; Luppino et al., 1994; He et al., 1995). However, proportions between premotor cortex and primary motor cortex differ consider-

ably between monkey (about 1:1) and man (about 17:3), illustrating that premotor cortex is the motor area with the greatest enlargement in humans relative to non-human primates (Von Bonin, 1944; Blinkov & Gleser, 1968). While monkey area 4 covers a substantial portion of the exposed surface of the precentral gyrus, it is pushed back into the depth of the central sulcus in humans, leaving the surface of the precentral gyrus to area 6 $\alpha$  (Geyer et al., 1996; Preuss et al., 1996). A less popular view suggests that rostral area 6 belongs to the primary motor cortex since it was found to be as excitable as area 4 (Penfield & Boldry, 1937).

**Area 44 and area 8** The monkey arcuate sulcus tags the border between granular prefrontal cortex and agranular premotor cortex, whereas in humans such a clear macro-anatomical landmark is missing. Even though the inferior and the superior precentral sulcus can serve as a gross orientation, two areas that lay in front of area 6, area 44 and the caudal portion of lateral area 8, are often conceived of as "premotor" or as transitional cortices between premotor and prefrontal areas. The homologies between humans and monkeys for these areas are especially difficult to determine. In the monkey, the ventral part of area 6 behind the lower ramus of the arcuate sulcus has been early divided into three parts by Vogt and Vogt (1919): areas 6 $\alpha$ , 6 $\beta$  and 6 $\gamma$ . Subsequently Bonin and Bailey (1947) designated areas 6 $\alpha$  and 6 $\beta$  as FCBm because they considered it to be the homologue of the human area FCBm (Economo & Koskinas, 1925) which in turn corresponds to Brodmann area 44. Based on two major architectonic features and the areas' topography, the cortex buried in the posterior part of the lower ramus of the arcuate sulcus (cf. area F5c, Matelli et al., 1985) is considered to be comparable with human area 44 (Galaburda & Pandya, 1982). As in humans, the monkey's area 44 (terminological assimilation as proposed by Petrides and Pandya (1994)) has a layer III that contains pyramidal cells which are largest in its deepest part. Layer IV of human area 44 is dysgranular, i.e., it contains only a few neurons, whereas in the monkey, this layer is difficult to discern at all. As in humans, monkeys' area 44 lies anterior to ventral areas 6 and posterior to area 45. Similarities on a functional level have been implicated by the discovery of mirror neurons which appear to code action-related information on a very abstract level (see chapter 4.4.3). As the human area 44, particularly in the left brain, is prominent in language functions, a common functional basis for area 44 in monkey and man may be vocal and non-vocal communication (Rizzolatti & Arbib, 1998).

In the monkey, stimulation of an area that lies within the rostral bank of the arcuate concavity triggers eye movements, and has therefore been termed *frontal eye field* or FEF. The frontal eye field encompasses and exceeds a caudalmost magnocellular portion of monkey area 8 and adjacent area 6, i.e. it does not coincide with any of the cytoarchitectonically defined areas, and it has not been labeled

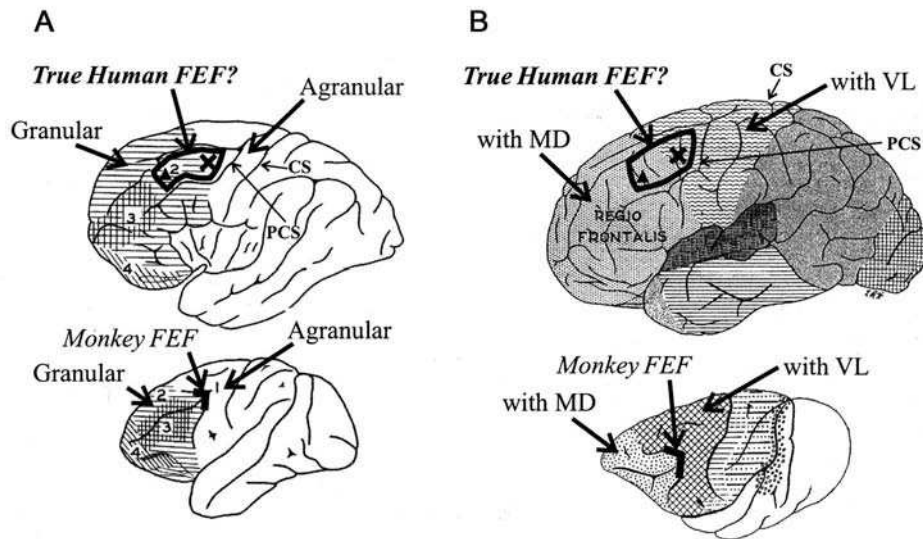


Figure 5.3: Putative localization of the frontal eye field (FEF) according to a comparison of basic cytoarchitectonic properties (A) and connections (B) in the human (upper panel) and in the monkey (lower panel) as reviewed and discussed by Tehovnik et al., 2000. Abbreviations: CS central sulcus, PCS precentral sulcus, MD connected with mediodorsal thalamic nucleus, VL connected with ventrolateral thalamic nucleus.

as an F-field in Matelli's premotor map. Both its topography and microstructure differ between monkey and man (Paus, 1996; Tehovnik et al., 2000, Figure 5.3). A striking difference is that the monkey frontal eye field lies mostly rostral to the precentral motor areas within the granular frontal cortex, whereas the human frontal eye field lies most probably within the agranular precentral cortex. While early stimulation findings suggested that the frontal eye field might match the posterior portion of the middle frontal gyrus in front of the precentral sulcus, imaging studies place the frontal eye field rather within the precentral sulcus and gyrus bordering the middle frontal gyrus and the superior frontal sulcus (Preuss et al., 1996; Tehovnik et al., 2000). As a rule of thumb, this region lies 20mm in front of the primary motor hand area (inverted omega) (Paus, 1996). However, the exact position of the human homologue to the monkey frontal eye field is still ill-defined. The same is true for the second frontal area related to eye movement control, the *supplementary eye field* or SEF. It has been discussed that in humans, this area lies within rostral SMA, whereas only human caudal SMA corresponds

to monkey field F3 (Grosbras et al., 1999). In this case, both frontal eye field and supplementary eye field have been considerably shifted during evolution.

**Premotor subdivisions** Homologies between human and monkey PMv and PMd are especially difficult to determine. This is partly due to the fact that in the monkey, cytoarchitectonic and microstimulation studies have provided conflicting evidence on the ventral-dorsal subdivision of the premotor cortex. The PMd-PMv boundary has been attributed either to the spur of the arcuate sulcus of the macaque (Rizzolatti et al., 1998, 2002, Figure 5.6 upper panel) or to the inferior arcuate dimple in the owl monkey, possibly corresponding to the inferior precentral dimple of the macaque (Preuss et al., 1996, Figures 5.4 and 5.5). In the former case, PMv would be larger than PMd, whereas in the latter case, PMd would be much larger than PMv. According to Preuss, the human homologue of caudal PMd occupies the precentral gyrus (corresponding to area 6 $\alpha$ ), whereas that of rostral PMd and area 8b occupies the dorsal frontal cortex rostral to the precentral sulcus (corresponding to area 6 $\beta$ ). Since both monkey PMv and human BA 44 are dysgranular (Bucy, 1944), and both monkey PMv as well as human BA 44 and/or ventral BA 6 represent upper limb and orofacial movements, Preuss proposes the human homologue of PMv to correspond to area 44 and the ventral part of area 6. In contrast, for Rizzolatti and co-workers (Rizzolatti et al., 1998, 2002, Figure 5.6) one important consideration is that during ontogenesis, human superior and inferior precentral sulcus develop from two separate primordia as vertical branches of the superior and inferior frontal sulcus (Turner, 1948). In view of functional differences between ventral and dorsal premotor cortex, it would be plausible to suggest this dual origin to be reflected in parallel functional differences. A crucial assumption here is that the functional areas delimited by the most ancient sulci maintain their basic location in phylogeny. This would imply that the human homologue of the superior arcuate sulcus is the superior precentral sulcus plus superior frontal sulcus. Then, dorsal area 6 $\alpha$  and 6 $\beta$  would correspond to F2 and F7, respectively (cf. Zilles et al., 1995). The human homologue of the inferior arcuate sulcus would be the ascending branch of inferior precentral sulcus plus inferior frontal sulcus. Finally, the descending branch of inferior precentral sulcus in humans would be equivalent to the inferior precentral dimple in the monkey, and hence, human ventral area 6 $\alpha$  and area 44 would correspond to F4 and F5 respectively. Rizzolatti and co-workers therewith propose that human PMd is located superiorly and PMv inferiorly to about  $z=51$  of Talairach space (see also Figure 6.2).

In contrast to the ventral-dorsal dissociation, SMA and preSMA could be non-contentiously differentiated on the basis of their cytoarchitecture and neurochemistry (Zilles et al., 1995, 1996). Cytoarchitectonic post-mortem investigations in

a sample of human brains shows that, SMA and preSMA separate roughly at the VCA line, and SMA and medial primary motor cortex at VCP (the vertical line passing the posterior commissure, perpendicular to AC-PC) (Vorobiev et al., 1998).



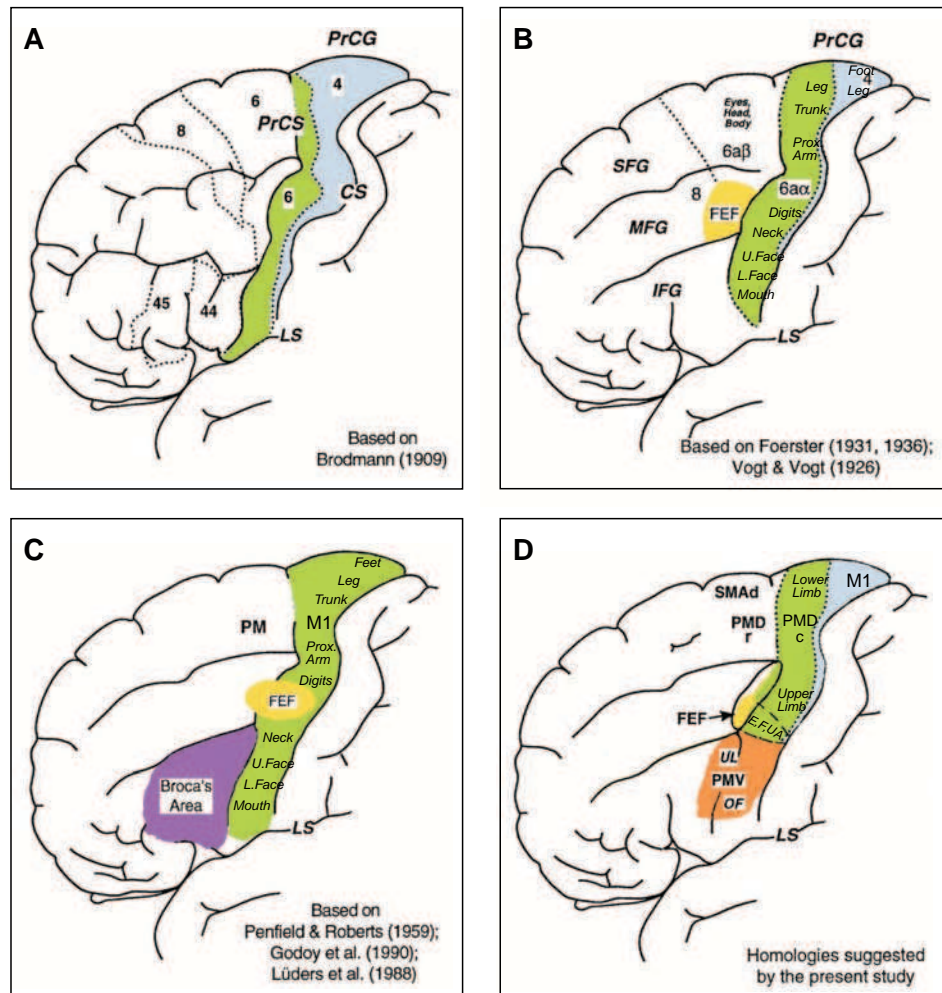


Figure 5.4: Alternative interpretations of the organization of the precentral motor cortex and the frontal eye fields in humans according to different studies and methods as reviewed by Preuss et al., 1996. Discrete somatic movements elicited by electrical stimulation are labeled by corresponding limbs. Note that these authors suggest that the border between PMv and PMd is at the level of the inferior frontal sulcus (panel D), whereas Rizzolatti and co-workers rather suggest it to be at the level of the superior frontal sulcus (see also Figure 6.2). Abbreviations: C central sulcus, E eyes, F face, FEF frontal eye field, LS lateral sulcus, OF orofacial movements, PrCG precentral gyrus, PrCS precentral sulcus, UA upper arms, UL upper limb.



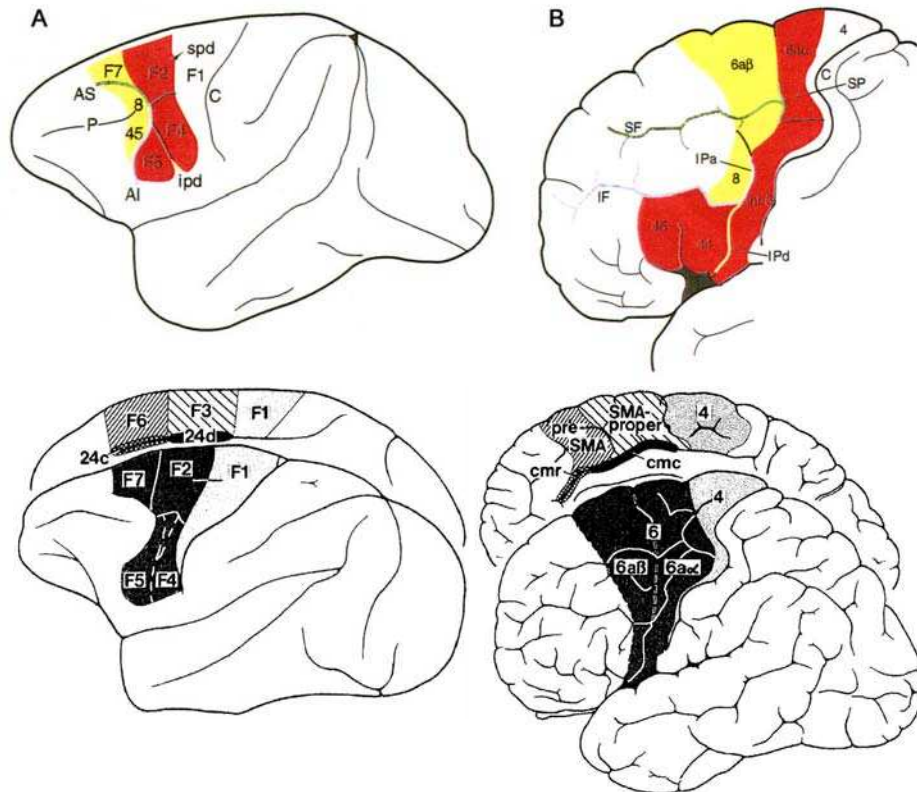


Figure 5.6: *Suggested homologies between monkey (left) and man (right). Rizzolatti and Arbib (1998) (upper panel) propose large portions of the frontal gyri to belong to the frontal motor areas. Particularly, these authors take BA 44 and BA 45 (extended Broca's Area) to be the homologue of monkey area F5. According to Zilles and co-workers (1995) (lower panel), human premotor area 6 $\alpha$  and 6 $\alpha$  $\beta$  correspond to monkey areas F2 and F7, respectively. Though authors do not consider ventral premotor sites, it is obvious from the figure that they do not take the human homologue of F5 to extend into BA 45.*

## Chapter 6

# Function

### 6.1 Patient studies

Studies of functional deficits following lesions that are explicitly restricted to the ventral portion of the lateral premotor cortex (or an area comprising PMv) have not yet been reported. Most often, lesions are localized within the dorsal premotor and/or the medial premotor sites. Lesions affecting the premotor areas can follow traumatic brain injuries or tumors, but are most often caused by stroke of the middle cerebral artery (which supplies blood to the lateral PM) or the anterior cerebral artery (which irrigates the medial and uppermost dorsal PM) (Figure 6.1).

Patients with stroke involving the PM have reduced functional (motor) outcome when compared with patients in whom the PM is spared (Miyai et al., 1999; Shelton & Reding, 2001), supporting the view that concerned movement representations shift from primary to premotor areas during recovery and a premotor compensation (Cao et al., 1998; Seitz et al., 1998; Byrnes et al., 1999; Johnson et al., 2002). As strokes occur more often in the middle than in the anterior cerebral artery, the upper limbs are typically more severely impaired than the lower limbs (this may also be the cause for rareness of studies on ventral premotor lesions). It is assumed that the recovery of isolated upper limb movements reflects small lesions of MI or the corticospinal tract, whereas recovery of only synergistic upper limb movements corresponds to a complete lesions of the same areas; however, if stroke patients do not show any significant upper limb motor recovery, an involvement of primary and large premotor lesions is to be suggested. Note that descending axons from primary motor cortex, premotor cortex and SMA must converge as they approach the internal capsule, so that even small subcortical lesions can cause tremendous impairments<sup>1</sup>. Conversely, lateral premotor areas

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<sup>1</sup>Since PM and SMA efferents run through the anterior half of the middle third of the corona radiata, but MI efferents to the posterior half, the exact location of a corona radiata involvement

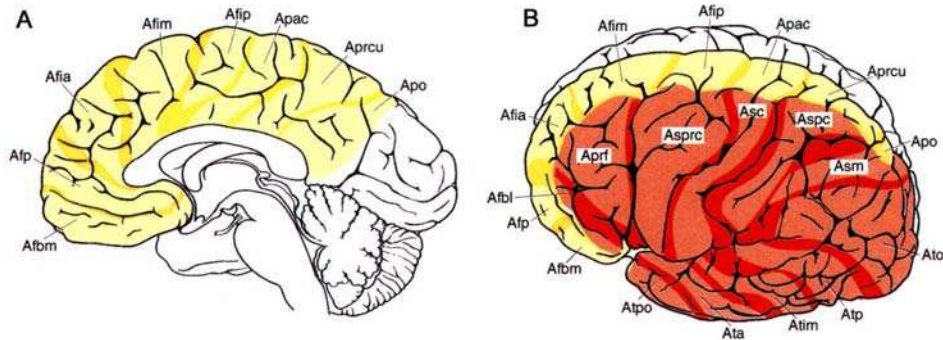


Figure 6.1: *The middle cerebral artery (yellow) supplies blood to the lateral PM, whereas the anterior cerebral artery (red) irrigates the medial and uppermost dorsal PM (Hartmann and Heiss, 2000).*

were found to be recruited for compensation in patients with Parkinson's disease during sequential and bimanual movements (Samuel et al., 1997). In this case, authors suggest that over-activity of the lateral premotor cortex, together with the parietal projections and cerebellum, reflect that patients use sensory (external) guidance to overcome impairments of internally guided movements.

Deficits following premotor damage have been exclusively described as far as motor output is concerned, which certainly has most significant and vital implications for the patient's everyday life. Generally, such motor deficits are worst in *sequencing*, that is, extended movement within which several single movements are integrated and coordinated in time. It therefore appears, as far as primary motor cortices are functionally intact, that not motor performance per se, but rather more general sequential representations are impaired in motor sequencing deficits following premotor lesions. The disintegration of serially organized movements was reported in connection with premotor lesions early on (Lurija, 1966; Derouesne, 1973). The quality of the sequencing deficits differs slightly with respect to the premotor lesion site. Premotor lesions that include parts of the SMA appear to impair sequential movements that are internally (memory-based), not externally, guided and often involve interlimb coordination (Dick et al., 1986; Lepage et al., 1999). Behavioral limitations caused by this brain damage in a subacute status are typically characterized by a paresis of proximal muscles (shoulder, hip) contralateral to the lesion side, and deficits in interlimb coordination. (Freund & Hummelsheim, 1984; Freund, 1985; Freund & Hummelsheim, 1985; Freund, 1990). In contrast, dorsolateral premotor lesions impair rather sensory guided sequential

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can be relevant as well. Affection of either corona radiata or internal capsule may also interrupt the facilitatory drive of PM and SMA that is provided by MI collaterals or from sensory afferents.

movement (Halsband & Freund, 1990; Halsband et al., 1993, 2001). These findings have been taken to indicate the suggested dissociation between externally and internally guided sequencing as realized within lateral and medial premotor sites, respectively (Mushiake et al., 1991, see chapter 4.4.5). Sequencing disorders are also one of the main indicators for apraxia, a deficit that often follows damage to either parietal or premotor regions (Liepmann, 1920; Harrington & Haaland, 1992). Sequencing deficits in planning and programming of volitional acts were described for several subtypes, e.g. limb-kinetic apraxia (Brown, 1972), or ideomotor apraxia (Kimura, 1982; Motomura et al., 1989; Rushworth et al., 1997). However, most obvious are sequencing deficits in apraxia of speech, which refers to a loss of the capacity to program the positioning of the speech musculature and the sequencing of muscle movements during volitional production of phonemes (Darley et al., 1969). The disintegration of learned articulatory gestures in speech apraxia has been specifically attributed to damage within the left PMv (Schiff et al., 1983; Ziegler, 2002). In a single-case study describing alexia and agraphia following a circumscribed surgical lesion in the left premotor cortex (area 6 superior to 44 referred to as "Exner's area"), striking functional dissociations point to a premotor role in the co-activation of precise sequences of motor and sensory activity patterns involved in reading and writing (Anderson et al., 1990).

## 6.2 Imaging studies

Current concepts on human premotor functions as have emerged from or are discussed in imaging research will be outlined in the following. Since concepts daring to exceed the standard formula of "motor preparation" are only sporadically discussed (and studies rarely target premotor functions as such), it is a major aim to provide evidence and explicitly verbalize the central views coming from this field of research. Concepts apply to functional-anatomical dissociations between right vs. left, medial vs. lateral, rostral vs. caudal, and dorsal vs. ventral premotor cortex, respectively. Studies targeting one of these differences refer to findings in the monkey premotor cortex to varying degrees. In general, right-left differences are mostly discussed independently of monkey research, whereas rostral-caudal and medial-lateral dissociations are usually tightly connected to the animal literature. Regarding ventral-dorsal differences, only one research topic in the monkey - the dissociation between more abstract sequence representations in the dorsal as compared to the ventral premotor cortex - has directly inspired imaging studies. Moreover, mirror neurons have caught attention and given rise to some imaging studies looking for a parallel action observation/execution matching system in humans. However, almost the entire body of ventral-dorsal differences that has emerged from imaging, and which may in fact be reconcilable with the monkey



literature as will be argued below, has been neglected. Note that in view of widely missing macro-anatomical borders between premotor subsections, labels like *ventral/dorsal* or *rostral/caudal* can only serve as a gross orientation. Views will be illustrated by some representative findings only, whereas in contrast singular findings that have not yet been replicated will be excluded.

### 6.2.1 Research issues and concepts

**Right versus left** Two concepts exist on hemispheric differences in premotor cortex. According to one, the right premotor cortex is more frequently engaged by spatial tasks, whereas the left premotor cortex shows a preference for non-spatial tasks. For instance, color cued responses activate the left PMv, spatially cued responses the right PMv (Hazeltine et al., 1997). A right premotor cortex dominance was reported for spatial working memory (Jonides et al., 1993; Haxby et al., 1994), spatial exploration (Gitelman et al., 1996), spatial body-centered judgment (Galati et al., 2001) and spatial attention (Gitelman et al., 1999; Kim et al., 1999). These findings may be seen in the light of the more general view that the right hemisphere is engaged in global as compared to local information processing on the perceptual level (Hellige, 1996). A different view on hemispheric specialization refers to effects of manual sequence learning when pure motor effects are balanced and controlled. Here, the left premotor cortex is taken to be dominantly involved during the acquisition of new motor sequences, even if performed with the non-dominant hand, whereas the right premotor cortex is rather involved in advanced learning stages and sequence storage (Schubotz et al., 2000; Toni et al., 2001; Grafton et al., 2002; Lafleur et al., 2002; Muller et al., 2002; Sakai et al., 2002). As far as complex sequences require more storage load than simple sequences, the storage hypothesis is supported by the finding that especially the right premotor cortex co-varies positively with the complexity (mostly the length) of sequences (Sadato et al., 1996). The same effect has been found in purely perceptual sequence learning (Schubotz & von Cramon, 2002a,c). Again, this concept may be seen as corresponding to more general concepts of hemispheric asymmetry that stress the right brain's role in sustained attention (Sarter et al., 2001) and enhanced interhemispheric exchange under high task demands (Banich, 1998).

**Medial versus lateral** Several imaging studies have investigated externally versus internally paced or cued movement in order to replicate a functional dissociation between lateral and medial premotor cortex in the monkey (Goldberg, 1985; Passingham, 1993). However, findings appear much more diverse in humans than in animals. Cunnington and colleagues (2002) report no lateral premotor activation either for internally or for externally triggered movements, but

medial premotor cortex for both. In contrast, Larsson et al. (1996) found lateral premotor cortex in both conditions, but medial premotor cortex in internally paced movements only. Several studies report both lateral and medial premotor cortex in both externally and internally cued conditions, though with different dominances (Wessel et al., 1997; Crosson et al., 2001; Weeks et al., 2001). Weeks and colleagues (2001) report both target areas to be enhanced in the internal manipulation. Wessel and colleagues (1997) find lateral dominance for externally paced conditions and medial activation for internally paced conditions, as expected from monkey data. However, the authors concede that enhanced activation within lateral premotor cortex could be caused by more movements in the externally cued condition. Finally, Crosson and co-workers (2001) also confirm medial premotor activation enhanced in internal (free) silent word generation and lateral premotor activation in the externally paced condition, respectively. Together, findings point to a principal trend for medial premotor cortex dominance in internally guided and lateral premotor cortex in externally guided movement. As in the case of hemispheric dissociations, this medial-lateral distinction can be seen in a broader functional context. Thus, the impact of the medial premotor cortex on internally guided as opposed to externally triggered movement supports the role of the fronto-median wall in action initiation and motivation (Seitz et al., 2000).

**Rostral versus caudal** In humans, as in monkeys, a functional rostral-caudal dissociation has been described predominantly for the medial premotor cortex, separating this area into the rostral preSMA and the caudal SMA proper, but the same distinction was recently also proposed to hold for lateral premotor cortex, especially PMd (pre-PMd versus PMd proper, Picard & Strick, 2001). Together, three functional trends are suggested to follow the considered rostral-caudal anatomical gradient, all of which can be seen as expression of a gradient from higher to lower levels of representation or behavioral control: One going from complex to simple execution, the second from intention to execution of action, and the third from early to late (sensori)motor learning stages. Considering the latter two dissociations, it appears that the rostral premotor cortex is involved earlier than the caudal one both in the narrow time scale (from intention to execution within a trial, Boussaoud, 2001; Simon et al., 2002) and in a wider time scale (from early to late learning stages within an experimental session, Iacoboni et al., 1998; Inoue et al., 2000). Note that all considered studies report rostral-caudal differences within the dorsal part of the premotor cortex, and all employ spatial tasks. In light of the spatial processing functions of PMd as opposed to PMv (see paragraph 6.2.1), it remains an open question whether the same rostral-caudal differences could be also found in PMv.



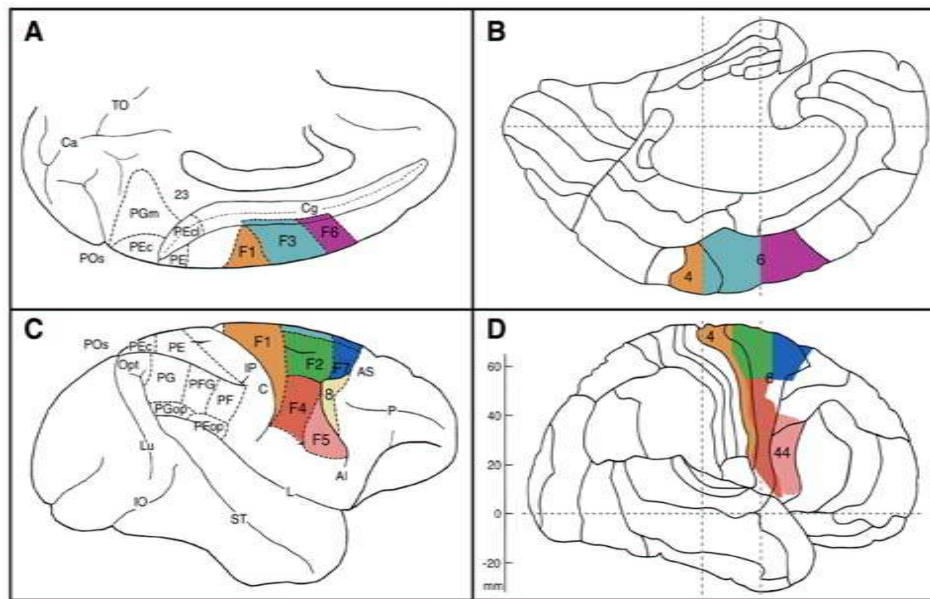


Figure 6.2: *F*-field homologies between monkey (A, C) and man (B, D) as suggested by Rizzolatti et al., 2002 (lower panels) and as summarized for the medial areas from different publications (upper panels). Based on functional evidence, it has been proposed that the human homologues of F5 and F7 to be located anteriorly, and F4 and F2 posteriorly to the inferior and the superior precentral sulcus, respectively. The border between ventral and dorsal PM, i.e., between F4 and F2, is suggested to correspond to level  $z=51$  in Talairach space (Talairach and Tournoux, 1988) in the human brain. Suggested homologies base largely on investigations of movement, but also on more recent evidence from perception of objects and actions.

**Ventral versus dorsal** As outlined in section 5.2, it has been proposed that human PMv and PMd are divided at the level of the superior frontal sulcus (Figure 6.2). If this view is adopted, then firstly, human PMv is proportionally much larger than human PMd, at least in its vertical extension. And secondly, the majority of the premotor activations reported in human imaging studies refer to PMv. Note that in most imaging studies, however, the labels "PMv" and "PMd" are used to denote premotor activations that are located inferiorly and superiorly to the (virtual continuation of the) inferior frontal sulcus, dividing premotor cortex in two fields of roughly the same size (cf. Figure 5.4, panel D). Hence, activations typically attributed to PMd may actually lay within the dorsal rim of PMv.

There is only one concept on ventral-dorsal dissociation of premotor cortex that has been explicitly tested. PMd is considered to code 'supramodal' sequences or action plans, whereas in contrast, PMv is taken to code the 'surface properties' of those sequences. Thus, a reliable effect across several imaging studies is that if only sequential complexity is increased, while leaving other features constant, PMd shows enhanced activity (Harrington et al., 2000; Boecker et al., 2002; Haslinger et al., 2002). However, a possible confound arises from the usage of response sequences that are arranged horizontally, as such response arrangements allow for sequences to be learned as spatial sequences, a problem addressed by the authors themselves. PMd may thus become engaged due to its function in space coding (see also paragraph 6.2.1). Moreover, as Hanakawa and colleagues (2002) have pointed out, a general interpretational problem arises from the fact that manual sequences can be coded by the assignment of numbers, for which visuospatial networks - including PMd - would also be expected (Simon, 1999). Authors discuss that PMd computes spatial information to manipulate mental representations as well as physical objects rather than coding abstract sequences. Hence, even if sequential complexity is manipulated in a finger opponent task (as for instance in Sadato et al., 1996), it can not be ruled out that PMd co-varies with spatial complexity rather than with 'abstract' sequence-specific complexity. Note also that Mushiake and co-workers (1991) are often cited in support of a sequence-specificity of PMd as opposed to PMv. However, though sometimes cited falsely, these authors report a set- and sequence-specific preference not in PMd as opposed to PMv, but rather in SMA as opposed to lateral premotor cortex. The spatial confound problem persists even in paradigms on 'abstract' sequential (or action) planning, which are typically using computer versions of the classical Tower of London (Hanoi) task. PMd activation reported in these studies may indeed reflect abstract planning, but those planning demands co-vary with spatial task demands that may require "imagined movement of the mind's eye and finger" (Baker et al., 1996). Of course this does not rule out the interpretation of existing imaging results in favor of amodal versus modal coding in PMd versus

PMv, respectively. This problem can be resolved by the investigation of complexity effects in non-motor sequential tasks that do not allow for numerical coding. In fact, results from those studies can be reconciled with (but do not necessarily imply) the supramodal/modal dissociation (Hanakawa et al., 2002; Schubotz & von Cramon, 2002a,c).

### 6.2.2 Background of own work

Dorsal-ventral differences in the monkey premotor cortex are most strongly characterized by a somatotopical representation that roughly parallels that in MI. Evidence has accumulated that this could also be true for the human. This becomes evident in movement-related behaviors, particularly under specific requirements of (skillful) control, (interlimb) coordination, (sensorimotor) integration, or specific cognitive demands. A somatotopical pattern emerges also across paradigms that require only the imagery or the observation of motion or action, i.e., in the absence of overt motor execution. In these paradigms, premotor correlates can be taken to reflect "covert (stages of) action" (Jeannerod, 2001), which as such would be expected to follow the same limb-dependent representation as overt action. Figure 6.3 shows the sagittal and the coronal distributions of activation coordinates from corresponding imaging studies.

However, only across a larger set of studies does it become obvious that in perceptual-attentional tasks in which neither the execution nor the imagination of action or movement is called for, premotor activations still appear to follow a somatotopy. This is most evident from covert spatial attention which engages PMd (or the dorsal rim of PMv) and object-directed attention which engages (inferior) PMv. The latter effect is particularly induced by tools, i.e., objects which implicate a specific, highly trained action, and therefore has been discussed as reflecting representations of action knowledge or object usage. As shown in Figure 6.3, spatial attention activates premotor areas which are also activated by arm movements and saccades, whereas object attention engages premotor fields typically engaged in hand and finger movements. Furthermore, body-referenced premotor activation is reported for imagery and observation of *non-biological motion*. Thus, PMd is typically reported for mental rotation, and inferiormost PMv (BA6/44) has been observed for the imagery of non-biological dynamic auditory stimuli (Figure 6.3). Activations may reflect the imagination of spatial manipulation using hands, arms and eyes, or covert vocal co-production (but see also Parsons, 2001).

Together, findings suggest that premotor cortex somehow represents not only imagined movement of one's own body, but also current or expected sensory features of the environment in reference to one's own body. The core suggestion of this account is not new in monkey research, though a specifically *dynamic* or *anticipatory* aspect has not been relevant in concerned studies. As outlined

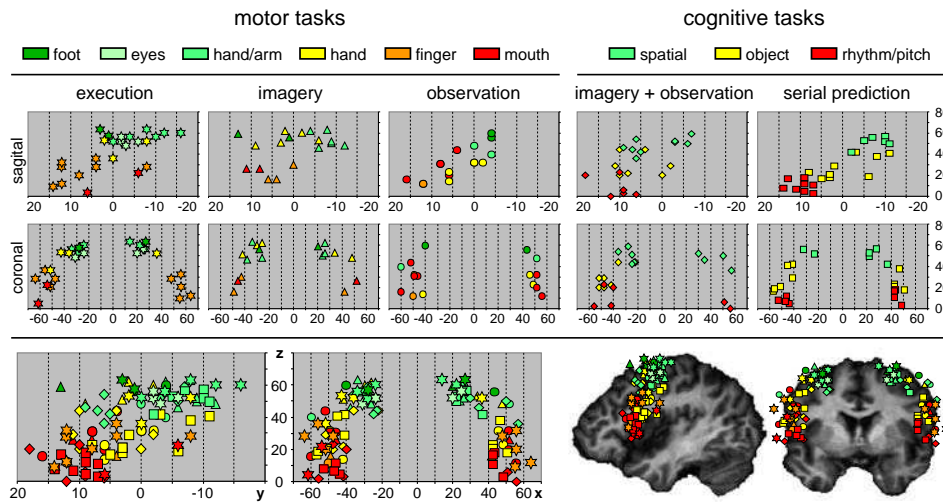


Figure 6.3: A Meta-analysis on recent imaging studies reveal a somatotopy of premotor activations in motor and in cognitive tasks. Talairach coordinates of premotor activation maxima are plotted as sagittal (y-axis/z-axis) distribution, neglecting the x-axis (first panel), the second panel shows the coronal (x-axis/z-axis) distribution neglecting the y-axis. Corresponding upper sagittal and lower coronal graphs show (from left to right) activation maxima as found during execution, imagery, observation of action or biological motion, the imagery and observation of non-biological motion and objects, and serial prediction. Color codes refer to different effectors in motor tasks, and to attended stimulus properties in cognitive tasks. All activations are summarized in a common schema in the lowest panel on the left side, and are also plotted on brain sections on the right side. Activations were taken from the following studies: Execution of action/biological motion: Anderson et al., 1994; Binkofski 1999; Corfield et al., 1999; De Jong 1999; Ehrsson et al. 2000a, 2001, 2002; Fox et al., 2001; Hamzei et al., 2002; Haslinger et al., 2002; Kawashima 1996; 1998; Kertzman et al., 1997; Kuhtz-Buschbeck et al., 2001; Lafleur et a., 2002; O’Driscoll et al., 1995; Sadato et al., 1996. Imagery of action/biological motion: Bonda et al., 1995; Decety 1994; Gerardin et al., 2000; Johnson et al., 2002; Lafleur et al., 2002 ; Parsons et al., 1995; Shergill et al., 2001; Thobois et al., 2000; Vingerhoets et al., 2002. Observation of action/biological motion: Buccino 2001; Campbell et al., 2001; Decety 1997; Iacoboni et al., 1999; MacSweeney 2000; Manthey et al., 2003; Von Cramon and Schubotz, 2003. Imagery and observation of non-biological motion and objects: Chaminade et al., 2001; Corbetta et al., 1993; Gerlach et al., 2002; Grabowski et al., 1998; Grafton et al., 1997; Griffiths, 2000a; 2000b; Halpern and Zatorre 1999; Lamm et al., 2001; Martin et al., 1995, 1996; Nobre et al., 2000 ; Ramnani et al., 2000; Vingerhoets et al., 2002. Serial prediction: Schubotz et al., 2000, 2003, in press; Schubotz and von Cramon, 2001a,b, 2002a,b,c.

above, monkey premotor neurons serve a variety of functions involving both sensory and motor representations. In registration to the monkey premotor body map, tactile receptive fields are arranged, often also anchored to visual receptive fields (review see Graziano, 2001) and, less frequently, to both visual and auditory ones (Graziano & Gandhi, 2000), probably reflecting the coding of environmental features as a reference frame for a particular set of effectors (Gentilucci et al., 1988; Rizzolatti et al., 1988; Fogassi et al., 1996). Therefore it has been proposed that premotor cortex represents *motor ideas* that may provide the basis for space representation, understanding actions and object categorization (Fadiga et al., 2000), that is in other words, cognitive functions. As a working hypothesis we therefore have suggested that neurons with sensory receptive fields for mouth, hand, and arm may account for the "pragmatic body map" that emerges from tasks like mental rotation, object categorization and music imagery. These tasks overlap in that they require the imagery of a dynamic scene or signal, but differ with respect to the environmental properties that are mentally manipulated or simulated in this way. For instance, the prediction of writing-like trajectories activates dorsal-most PMv, that of pointing-like trajectories the middle PMv (Chaminade et al., 2001), and learning auditory event prediction correspond to an increase in inferior-most PMv (Ramnani et al., 2000). Each of these tasks corresponds to sensory events that are usually caused by or engaged in movement of arm and eyes (spatial locations and orientations), the hand and fingers, sometimes mouth (object properties), or the vocal effectors (auditory and rhythmic features). The possible existence of such a pragmatic body map and the hypothesis that premotor cortex might serve as an internal forward model of environmental dynamics has been systematically investigated in a series of fMRI studies, as will be outlined in the following last part (III).

## **Part III**

# **Own work**



## Chapter 7

# Introduction

The aim of this chapter is to give a short summary of a series of studies, in most of which fMRI was used to investigate non-motor functions of the human premotor cortex. Studies will be largely ordered chronologically so as to outline the train of thought that motivated each of them.

In order to investigate which factors modulate activation within the premotor cortex in the absence of motor requirements, we introduced the *serial prediction task (SPT) paradigm* (Schubotz, 1999). As a perceptual counterpart to the serial reaction task (SRT, Nissen & Bullemer, 1987), it requires subjects to extract and predict repetitive sensory patterns within sequentially presented stimuli (*sequencing*). In contrast to the SRT however, the SPT does not require motor co-production; that is, stimuli are not given any explicit motor significance (but see Experiments 2 and 3 for implementation of a SRT). Instead, performance in instructed sensory pattern prediction is tested after stimulation by a forced choice judgment on the occurrence of a sequential violation. Hence, sequencing is induced on an explicit and purely perceptual level (see Figure 7.1). Of course, non-motor functions can only be investigated if behavioral responses are discarded as far as possible. The number and quality of the responses required in the SPT, one button press per trial indicating either *sequence violation* or *no sequence violation*, are balanced between compared conditions; moreover, responses do not occur in the phase in which the MRI signal is analyzed for task effects, but several seconds thereafter. Given this form, the SPT can be realized in many different ways. First, it can be presented in the auditory or in the visual domain, and even tactile stimulation would be conceivable (though this has not yet been done). Second, sequential structures can be repetitive, monotone, or hybrid, they can be very complex or very simple; using this parameter, any level of difficulty can be generated from chance up to optimal performance. Third, participants can be instructed to attend to different properties, e.g. sequences of pitch, rhythm,



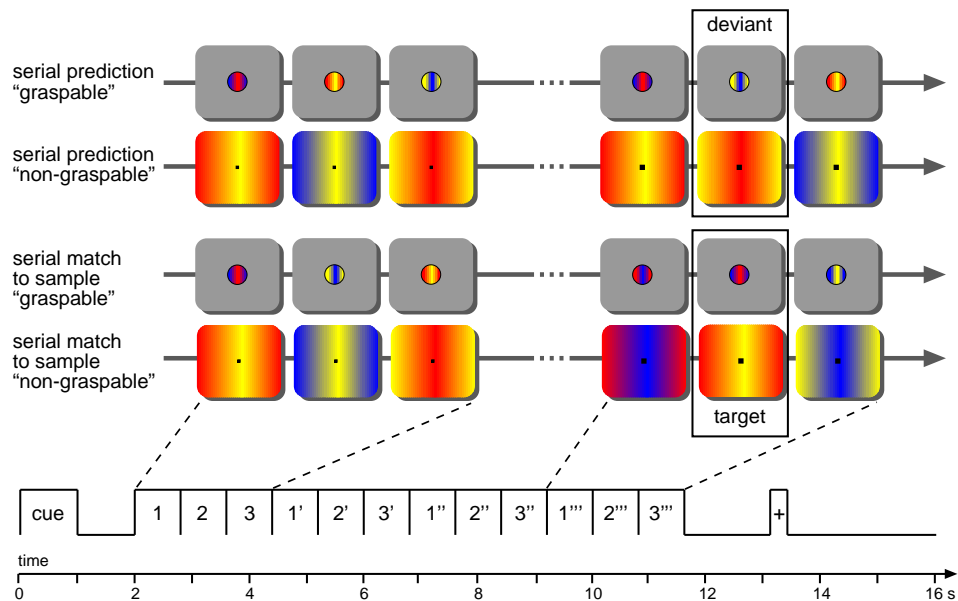


Figure 7.1: Example for the serial prediction task (SPT) paradigm (Schubotz and von Cramon, 2002b). A sequence of stimuli is presented either in the visual or in the auditory domain. In most studies, the stimulus material is abstract in order to avoid co-activations by semantic or episodic memories. A typical trial length is 6s, with an inter-trial-interval of 6s to 8s. The stimulus sequence is temporally structured, consisting in either repetitive, monotone or combined repetitive and monotone sequences. Complexity and thereby task demands can be varied on different levels, for instance by sequential structure, by sequence length, or by discriminative perceptual demands. Sequential structure is provided only within the attended stimulus property (e.g. the pitch of a tone sequence) whereas other stimulus properties are presented in randomized order (e.g. the spatial sources of tones or their temporal duration). In half of all trials, sequences contain a sequential deviant within the last sequence elements, that is, the order of two elements is flipped. Subjects are asked to attend to a specific stimulus property, for instance to color, orientation, or pitch, while ignoring other features, and to find out how the sequence will evolve further on. At the end of a trial, subjects have to indicate in a forced-choice mode whether the sequential order of the to-be-attended stimulus property was correct until the end of presentation, or whether it was violated. As control tasks serve those which provide the same amount of physical information without requiring the identification and prediction of a sequential structure. This can be for instance a target detection task, or a serial-match-to-sample task (as given in the example above). In a serial-match-to-sample, the first stimulus in a trial (probe) has to be remembered and to be compared with each of the following stimuli. Subjects are requested to indicate if the same stimulus reappears (target) or not.

form, color, size, surface, position, orientation, distance, intensity or sound quality. Why has the SPT paradigm proven to be such a powerful tool to investigate non-motor functions of the lateral premotor cortex? Premotor areas are engaged in the SPT for the same reason as they are activated in the SRT: because of their role in sensory guided movement, and more specifically in the transformation of sensory events into motor events. Animal literature and imaging data indicate that premotor computations necessarily precede any overt and voluntary motor performance, but premotor activation does not have to result in overt movement. This issue will be considered in the last chapter (9). The two most relevant features of the SPT are, first, the continuity of stimulation and, second, the instructed prospective attention. Due to these features the SPT parallels basic requirements of voluntary action: it has to be performed smoothly, i.e., under anticipation, and so has sensorimotor transformation.



## Chapter 8

# Premotor cortex in non-motor tasks

### 8.1 Motor areas in rhythm perception

In Experiment 1 (Schubotz et al., 2000), an auditory and a visual "rhythm monitoring task" (later more generally referred to as *serial prediction task*) was employed to investigate whether a purely perceptual rhythm task induces activation within the frontal motor areas. Both tasks were contrasted with modality-matched deviant detection tasks that did not require the processing of sequential features and that were perceptually balanced. Though this study was basically explorative - since at this time no single imaging study on a non-motor rhythm task was published - our hypotheses targeted the motor areas. This was motivated twofold. First, using event-related brain potentials we had found a rhythm task to engage bilateral posterior frontal sites (Schubotz & Friederici, 1997; Schubotz, 1999). We suggested that right and left BA 44 could be the sources of these slow potentials, or even more posterior sites within BA 6. Second, timing functions were thought to be primarily domiciled in the domain of motor preparation and performance, as also reflected by the fact that timing was usually investigated by tapping, interval production or rhythm production tasks. A further aim of this study was to implement a time perception task that was as natural as possible, i.e., rather continuous (rhythms in the several-seconds range) than discrete (single intervals in the millisecond range), and at the same time a task that did not allow for verbalizing strategies. Our findings yielded significant activations within bilateral BA 6/44, in the SMA, and the cerebellum in both the auditory and the visual rhythm monitoring, as compared to deviant detection. We discussed SMA activation in view of its function in sequencing and preparation. For BA 6/44, non-language functions of Broca's Area were focused on, particularly hierarchical, general sequential pro-

cessing (Grossman, 1980; Fuster, 1995; Lieberman, 1991). Our data confirmed prior studies on perception of linguistic and non-linguistic temporal patterns (Fiez et al., 1995; Plathel et al., 1997) as well as temporal orientation (Coull and Nobre, 1998). We cited a study on Broca's role in tongue movements (Fox et al., 1988), which placed emphasis on the supra-linguistic character of this function rather than on a somatotopical specificity relating somehow tongue movements to rhythm perception or production. However, this latter idea become more important for us in the following, and so we set out to investigate it in a follow-up study (Experiment 4). At the same time, the engagement of areas conceived of as classical motor cortices in a purely perceptual task, with motor responses balanced between contrasted conditions, was suspect to some reviewers. The next study (Experiment 2) therefore investigated the influence of motor requirements on sequential processing.

## 8.2 Instructed motor significance

From a formal perspective, sequences have ordinal and interval properties, i.e., a temporal order and a temporal spacing (rhythm, timing), and these two properties may be reciprocally dependent (Dominey, 1998) or not (MacKay, 1987a,b). In Experiment 1, we had investigated neuronal correlates of the processing of interval properties; Experiment 2 (Schubotz & von Cramon, 2001b) approached the comparison between these and the second basic feature of sequences, ordinal properties. We tested the hypothesis that attention to interval and ordinal features induce different premotor activations. To this end, we implemented ordinal properties by spatial features, and not, as would also have been possible, by object-specific features (see Experiment 4). The second purpose of Experiment 2 was to manipulate the motor significance of a presented sequence, referring to the suggestion that motor timing and perceptual timing share the same neural architecture (Rosenbaum, 1998; Schubotz et al., 2000). We introduced a cue that indicated, firstly, whether interval or ordinal properties were to be attended, and secondly, whether a sequence was to be monitored for deviants or to be reproduced manually thereafter. Hence, using one and the same visual stimulation, only instructional cues differentiated tasks and corresponding brain activation. As a result, we found dorsal and ventral premotor areas to be engaged preferably in spatial-ordinal and in rhythmic-interval processing, respectively, with the latter finding being a replication of Experiment 1. Regarding motor significance, we found primary motor and corresponding cerebellar activation to co-vary positively with the requirement to reproduce a sequence in contrast to the perceptual monitoring of the same sequence, regardless of whether ordinal or interval features were attended. In addition, preSMA and SMA were significantly more engaged

before reproduction than before monitoring. This anatomical effect was found to be property-specific, with preSMA engaged before interval production and SMA before ordinal production. Results indicated premotor areas to be dissociated by attended stimulus properties rather than by motor significance of stimuli. Particularly, they reinforced the assumption that the correlation between the attended stimulus property on the one side and the sensorimotor function of the respective premotor subregion on the other side might somehow be related along a rough somatotopical pattern. This assumption motivated Experiment 4.

### 8.3 Attention to motion

Experiment 3 (Schubotz et al., 2000) aimed to investigate to what degree premotor activations in the SPT were due to mere attention to motion. Although on a perceptual level, experimental and baseline conditions had been balanced in the preceding experiments, we could not exclude a priori that in the baseline condition *motion information* was processed on a more superficial level than it was in the SPT. Accordingly, Experiment 3 implemented a baseline condition that required strict attention to motion in both the baseline task and the SPT condition. In the former, participants were asked to track a guiding stimulus by stepwise saccades. In the SPT, the guiding stimulus moved in a spatially predictable and rhythmic manner; participants were asked to encode the rhythm during guided saccades and to indicate rhythmic deviants in a second recall phase. Rhythmic violations of the tracked motion in were to be indicated immediately after detection. In the baseline condition, participants had to indicate immediately whether the tracked stimulus turned into a target stimulus. We employed stimuli that are usually used to determine visual acuity, so-called Landolt Rings, i.e. rings with small openings on top, bottom, right or left. Targets were those with a bottom opening. A second aim of Experiment 3 was to test whether lateral premotor cortex and SMA would be engaged differently during the encoding of a sequence and the sequential recall. As outlined above, findings in the monkey propose the former to be more strictly dependent on external rather than on internal guidance, and the opposite to be true for the latter. Accordingly, we expected a dissociation between medial and lateral premotor sites for earlier and later stages of the SPT task (Goldberg, 1985; Wise & Mauritz, 1985; Passingham et al., 1989; Halsband et al., 1993, 1994). Our results (Figure 8.1) demonstrated premotor activation in the SPT condition as compared to the baseline task, even though attention to motion, preparatory, saccades-related and response-related requirements were entirely balanced between these conditions. We therewith could exclude the interpretation that premotor activation during the SPT was simply due to attention to motion. With regard to the second question, we found that learning was reflected

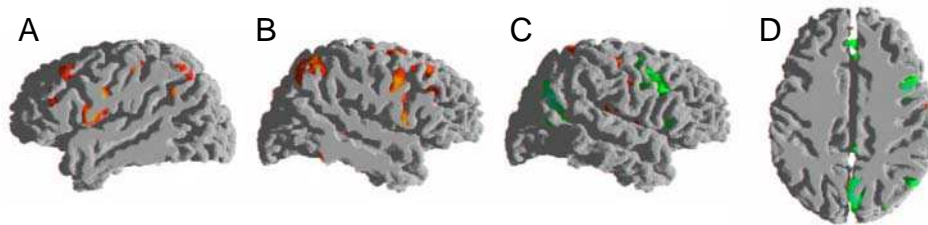


Figure 8.1: *Premotor activation during rhythm encoding (A and B) in a serial learning saccades task, as in contrast to a saccades tracking task. C and D: rhythm recall as a direct task contrast between encoding (red) and recall (green). In this phase, activation shifted to the right hemisphere.*

by two activation shifts: one from the posterior to the anterior medial premotor cortex, i.e. from SMA proper to the preSMA, and the other from the bilateral to the right lateral premotor cortex. We discussed the right hemisphere dominance in the context of grouping local (fragmented) information to global (linked) information (Kosslyn et al., 1990).

## 8.4 Property dependence

In Experiment 4 (Schubotz & von Cramon, 2001a) we aimed to investigate to what degree different perceptual properties of sequences draw on different subsections of the lateral premotor cortex. We started with the assumption that the processing of sequential information is of vital meaning when dynamic information, i.e., environmental movement is processed. From a logical point of view, a visual sequence is determined by three and only three properties: time, space, and quality. We therefore employed a serial prediction task that provided rhythmic, spatial, and object-related sequential information in one and the same visual stimulation. The anatomical hypotheses were motivated by both animal and human literature, and integrated two observations: first, that the premotor area contains a body representation roughly organized in parallel to the primary motor cortex; and second, that the premotor cortex is involved in sensorimotor mapping (Mushiake et al., 1991; Halsband et al., 1994). We hypothesized that attention to different sensory properties should engage premotor fields that are used to transform those sensory patterns in a corresponding motor pattern. In contrast to later studies, we stressed the idea of sensory guidance, as in contrast to that of action planning in terms of sensory effects (see also chapter 8.12 and 8.13). As a result, we found a left-hemispheric network comprising of ventral premotor cortex, preSMA and

anterior intraparietal sulcus to be commonly engaged in all sequences, relative to baseline. We argued that this network could reflect the human homologue of a premotor-parietal *grasping circuit*, activated due to sustained attention to objects (see also Experiment 5). In addition however, specific responses were found in bilateral BA 6/44 (for rhythm), in left ventral premotor cortex (for objects) and in bilateral dorsal premotor cortex (for space). Two alternative (but not reciprocally exclusive) interpretations were discussed. The first was that lateral premotor sites, are incrementally sensitive from dorsal to ventral PM to the sensory guidance by spatial, object-related and temporal parameters. This interpretation was basically motivated by the medial versus lateral dichotomy for internally versus externally guided behaviors. However, we favored the alternative interpretation that our findings reflected a body-referenced representation of attended environmental dynamics (Rizzolatti et al., 1987b; Greenfield, 1991; Murata et al., 1997), what we later referred to as *habitual pragmatic body map* of the lateral premotor cortex. Experiment 4 gave rise to a number of questions and follow-up studies.

## 8.5 Graspability

Ventral premotor activation had been reported for a variety of object-related tasks, such as object grasping (Matsumura et al., 1996), imagining object grasping (Decety et al., 1994; Grafton et al., 1996), action-word generation (Martin et al., 1995), looking at tools (Grafton et al., 1997), and memorizing graspable objects (Gruenewald et al., 2000). In all of these paradigms, real objects, or pictures or drawings from real objects had been employed. A major question deriving from Experiment 4 was therefore, how abstract, non-natural geometrical figures could engage a grasping circuit for real objects. Moreover, the stimulus material employed in Experiment 4 was made up of circle-shaped figures of homogeneous size that differed only with regard to their colors and the form of their inlays. Accordingly, since such stimuli did not have any *pragmatic properties* or *motor significance*, it could hardly be argued that object sequences corresponded to sequences of covert grip configurations. But to what degree, then, could the premotor hand field be specifically interested in object properties of predicted sequences? Experiment 5 and Experiment 6 (Schubotz & von Cramon, 2002b) were designed to approach this issue. Two factors were manipulated: the task, requiring sequential processing or not, and the stimulus material, being more or less "graspable" by overall size or parcelling. Data yielded the task to be of major influence on premotor activation, which showed up only in the serial prediction requirement. In contrast, object features that were thought to relate somehow to motor significance did not cause any difference in premotor activations. We concluded that the significant correspondence between objects/figures and premotor hand field, as



revealed by activation, must be one on a very abstract level of representation (see chapter 8.12). Seeking a framework describing this view, we adopted the term *dynamic context* as compared to *pragmatic context*. We proposed that, whereas natural objects are embedded in a pragmatic context and hence have their "own" habitual affordance, abstract objects might engage the very same network in a dynamic context as this usually has a vital meaning. Alternatively one could assume that in premotor cortex, attended objects are represented as a selection of very abstract - and hence generally applicable - feature fragments (like e.g. edges of different orientation and so on). Conversely, then, arbitrary properties like color or surface that are missing a definite motor significance could be represented within premotor sites.

## 8.6 Property-specific complexity

Experiment 7 (Schubotz & von Cramon, 2002c) was motivated by a behavioral confound in Experiment 4 (chapter 8.4): The performance levels differed between the three experimental conditions in an order that paralleled the anatomical distribution of activation, with the spatial task being easiest and the rhythm task being most difficult. Experiment 7 aimed to de-confound effects of attended stimulus property on the one hand and task difficulty on the other. The concept of load has been an important approach in investigating the cerebral correlates of working memory: Only that area which is specifically involved in the considered function should show enhanced activation when the task gets more difficult (Braver et al., 1997; Rypma & D'Esposito, 1999; Rypma et al., 1999). Capitalizing on this rationale, we implemented a pitch prediction task and an object size prediction task of low, middle, and high sequential complexity. The present study was a very strict test of the assumption derived from our previous studies: We hypothesized the premotor hand field to co-vary positively with the size sequences, but not with pitch sequences, whereas the opposite should be true for the premotor vocal field (BA 6/44). Note that, formally, both the auditory and the visual tasks implemented the same monotone, repetitive, and hybrid-monotone sequences, and hence were balanced with regard to requirements on each level of task difficulty. As in preceding studies, control task conditions matched the experimental task with regard to the stimulus material and the overall trial structure, but did not require sequential processing. Instead, participants were asked to indicate pre-defined target stimuli. Results confirmed our hypotheses (Figure 8.10 left panel). Data showed that activation within premotor areas does not depend on behavioral effort or task load per se, but is systematically related to the predicted stimulus property. Moreover, since activation co-varies with the difficulty of serial prediction, findings also confirm that modulations of premotor areas can occur in the

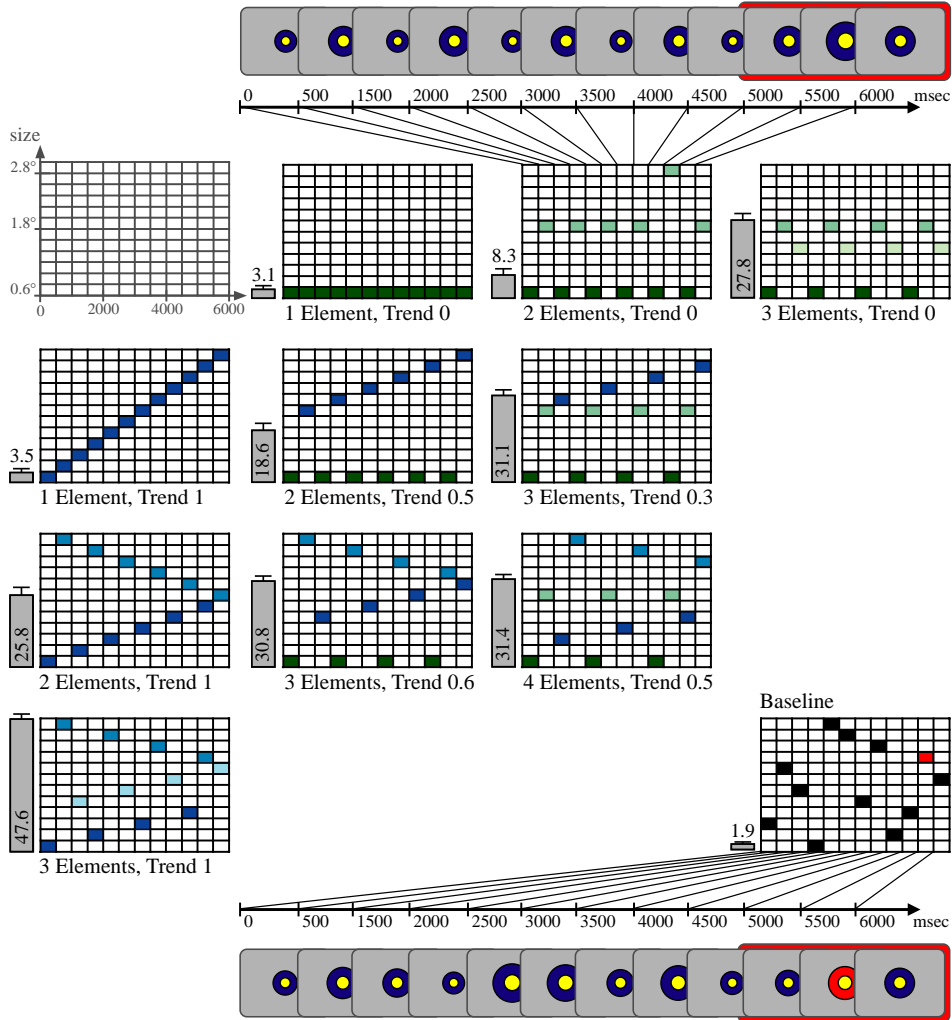


Figure 8.2: Schematic examples of all types of stimulus sequences and corresponding error rates in Experiment 8. For each sequence type, a size by time diagram shows a typical course of one trial, composed of 12 pictures presented for 500ms each. Elements with a trend of zero (green) and elements with a constant positive trend (blue) were taken to build 1-, 2-, 3-, and 4-element sequences. The 1st, 2nd, 3rd, and 4th element within a sequence are indicated in different shades of the corresponding color. Examples for the visual presentation are shown for one serial prediction condition (top panel) and the baseline condition (bottom panel). In the sequence conditions, participants were asked to build up expectations about the last three stimuli of a trial (as highlighted in red in the figure). In case of successful serial prediction, participants were able to indicate whether any stimuli deviated from the sequential pattern introduced by the first nine stimuli within a trial. In contrast, sequential order was irrelevant to indicate color deviants, as required in the baseline condition. The gray bars on the right side of the schemata display the mean error rates and the standard errors in the corresponding conditions.

absence of changing motor requirements. Discussing these findings, we proposed an extension of the concept of an “action observation/execution matching system” to be located in the ventral premotor cortex, as discussed by Rizzolatti and Arbib (1998). We pointed out that the lateral premotor cortex may rather be more generally engaged in the mapping of perception onto motion (not only observed actions onto imagined actions), especially when trying to predict the future course of a dynamic event.

## 8.7 Parameters of complexity

Simultaneously to the construction and implementation of Experiment 7 (chapter 8.6) statistical analysis for fMRI methods were improved and for the first time data could be analyzed in a parametric design. In a direct follow-up study (Experiment 8) (Schubotz & von Cramon, 2002a), ten levels of complexity were realized for a size sequence task which was identical to that employed in the preceding study, but this time using a regressor model. We pointed out that increased activation within motor areas during the serial reaction task (Nissen & Bullemer, 1987) as reported in other fMRI or PET studies (Grafton et al., 1995; Hikosaka et al., 1996; Sadato et al., 1996; Hazeltine et al., 1997; Gordon et al., 1998; Honda et al., 1998; Hikosaka et al., 1998; Sakai et al., 1998; Toni et al., 1998) always had confounded sequential complexity on the perceptual and on the motor level. Due to our prior findings, we suggested that increasing the complexity of a to-be-predicted sequence should increase premotor activation in the absence of motor demands. We manipulated complexity systematically on two factors: sequential length and sequential trend (see Figure 8.2). Whereas the former refers to the standard manipulation of sequential complexity, the latter intended to mimic dynamic patterns we typically face in everyday life, like for instance when attending to approaching and departing objects. As a result, we found the left ventral premotor cortex to be the only frontal area that co-varied positively with both behavioral (error rates) and stimulus-driven (sequential length and trend) measures of complexity. Interestingly, parametric effects of complexity were found to draw on the right premotor-parietal network, a finding that we discussed in the context of the right brain’s advantage for global processing (cf. chapter 8.3). While the main effect of activation was located in the ventral premotor section, as in the preceding study (chapter 8.6), increasing the sequential length increased activity in more extended dorsal premotor regions. This additional recruitment was discussed from different perspectives, especially with reference to a stimulus feature that might have triggered networks for space coding.

## 8.8 Modality dependence

A further question following from Experiment 4 (chapter 8.4) was whether sensory modality of predicted sequences would have a significant influence on premotor activation. As discussed in chapter 4.3 somatosensory and visual responses prevail in the monkey premotor cortex, whereas auditory ones appear to be either negligible or rarely investigated. However, we had already found premotor activation for auditory sequences (Exp. 1 and 7). Furthermore, our findings pointed to a dissociation between properties that were potentially guiding (or following) actions of different motor effectors, and this should not be different in principle for auditory and visual stimuli. On the other hand, all tasks in Experiment 4 shared a common network in addition to the property-specific activations, and this common activation could reflect modality-specific influences. Accordingly, Experiment 9 (Schubotz et al., 2003) was a auditory replica of (visual) Experiment 4. We implemented a rhythm, object, and spatial serial prediction task, and a target detection baseline condition. Using the same trial and task parameters only the stimulus material was exchanged. As in the visual version, stimuli were artificial, i.e. non-natural sounds. Results replicated those of Experiment 4 and re-confirmed a habitual pragmatic body map for sensory events in the lateral premotor cortex. As in Experiment 4, dominant activation was found in the ventral premotor vocal field for the rhythm task, in ventral premotor hand field for the object sequences, and in dorsal arm/eye field for the spatial sequences (Figure 8.8). In addition, all auditory tasks also shared a common premotor-parietal network, one that differed from the visual one of Experiment 4 with regard to its location (Figure 8.10, right panel). Together, Experiment 4 and 9 suggested that premotor activations reflect both the pragmatic stimulus properties in reference to different body parts, and independently and additionally the sensory modality that is attended to. Particularly, patterns indicated that the inferiormost PMv is engaged in auditory prediction, whereas the middle PMv is engaged in visual prediction. However, an alternative and more parsimonious interpretation remains to be tested, and this is that there is an obligatory processing of object properties in visual sequences and an obligatory processing of rhythm in auditory sequences, even if participants are asked to ignore these features. According to this view, there would be only one factor determining premotor activation sites: pragmatic stimulus properties.

## 8.9 Action observation

Our findings suggested that the prediction of serial events draws on that motor effector that would be used habitually to produce such events as action effects.



Figure 8.3: *Example of movies presented in the action observation conditions in Experiment 10. The upper panel shows a correct action (setting an alarm clock), the second panel an object error (brown shoe cream is chosen for the black shoe), and the third panel shows a movement error (coin is held in wrong orientation to the opening of a piggybank). The lower panel shows an example of the control condition (aimlessly moving around a scotch tape roll).*

With Experiment 10 (Manthey et al., 2003) we intended to approach this idea in a new way by presenting movies on manual actions towards objects that did or did not contain action slips (see Figure 8.3). Asking participants to judge whether actions were correctly performed or not, we tested whether action observation would elicit activation comparable to the object-specific serial prediction tasks. Note that presented actions were typically not completed at the end of the movie, and therefore required the *prediction* of action course, similar to the serial prediction task. We argued that manual action prediction should engage premotor hand fields. Moreover, since actions should be represented by two basic informations, the movement and the target object or aim, we designed experimental conditions that drew on these two different properties: object-related and movement-related action slips. As a result, we found ventral premotor cortex, together with corresponding parietal regions, to be activated by action prediction. Errors that concerned the involved objects were found to enhance activation within the same areas of the left hemisphere, whereas movement-related errors rather drew on the right premotor cortex. The former result was interpreted as reflecting the left brain's dominance in right handers, as object manipulation is performed mainly with the right hand. For the latter result, we suggested prolonged perceptual analysis required in this experimental condition to engage specifically the right hemisphere. Most importantly, however, we found premotor activation during action observation to be located in BA 6 (at the border to BA 44) rather than in Broca's Area (BA 44 proper or even BA 44/45), as had been suggested by other authors (Iacoboni et al., 1999). This finding implied that one of two views has to be relativized: either, that BA 44 is *the* human homologue of monkey's area F5c; or, that only BA 6/44 (as in contrast to the rest of lateral premotor cortex) is engaged in the analysis of observed actions. This was approached in the next study.

## 8.10 Action observation and sequencing

A follow-up study (Experiment 11, Von Cramon & Schubotz, 2003) directly tested whether our findings on lateral premotor cortex would be compatible with one of the most influential recent findings in the monkey brain: the discovery of the *mirror neurons* (see chapter 4.4.3). This premotor *resonance* was suggested to reflect a direct mapping of an observed action onto an internal motor representation of the same action, and thereby to lead to action understanding. Using this brain response as a criterion, we tested the hypothesis that the prediction of sequential sensory patterns suffice as a model for understanding actions. In Experiment 11, we implemented both an object-specific serial prediction task (comparable to those employed in Experiment 4, 7, and 8) and an action prediction task (comparable to that employed in Experiment 10), together with two corresponding control

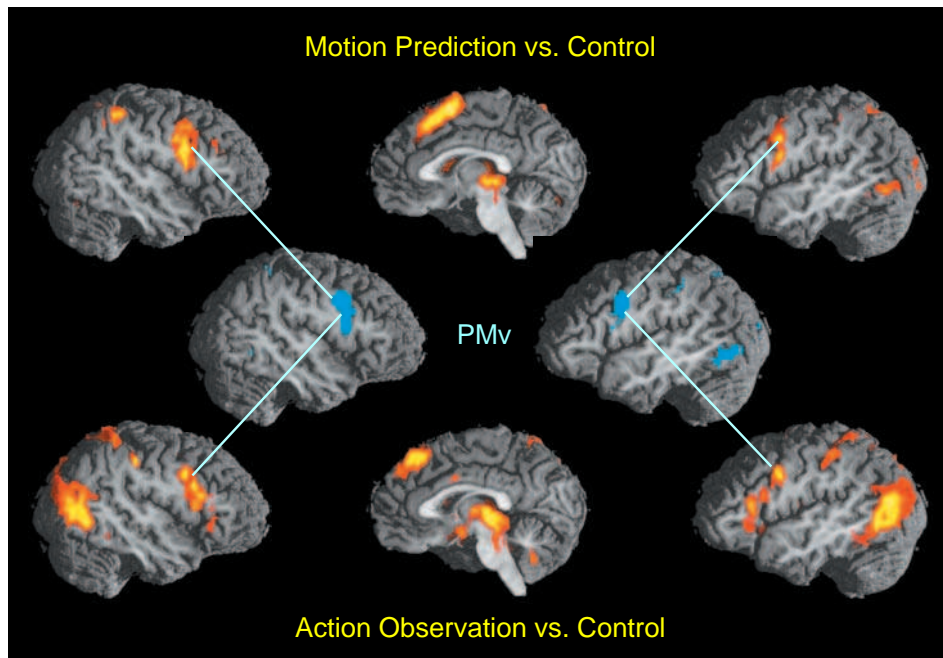


Figure 8.4: *Activation during action observation and a serial object prediction, each contrasted with a common baseline task (Experiment 11). The middle panel shows voxels that were significantly activated in both contrasts (blue), indicating that both conditions overlap in BA 6 of the ventral premotor cortex (PMv), but not in BA 44 (Broca's Area).*

tasks. Findings showed the action and the sequence condition to overlap significantly in bilateral ventral area 6 of the premotor cortex (Figure 8.4). In addition, action observation and the movement observation baseline task elicited activations within right and left BA 44. With regard to the common BA 6 activation, our findings pointed to a much more basic account of the premotor 'resonance' towards actions as previously assumed. Understanding an action rather appeared to be a special case of predicting a future event announced by ongoing sequential sensory patterns. With regard to the BA 44 activation, however, present findings allowed two interpretations: either, that Broca's Area is involved not only in goal-directed actions, but even in non-goal-directed movements; or that our control condition inspired participants, without being asked, to think about potential actions. These interpretations remain to be investigated in future studies.



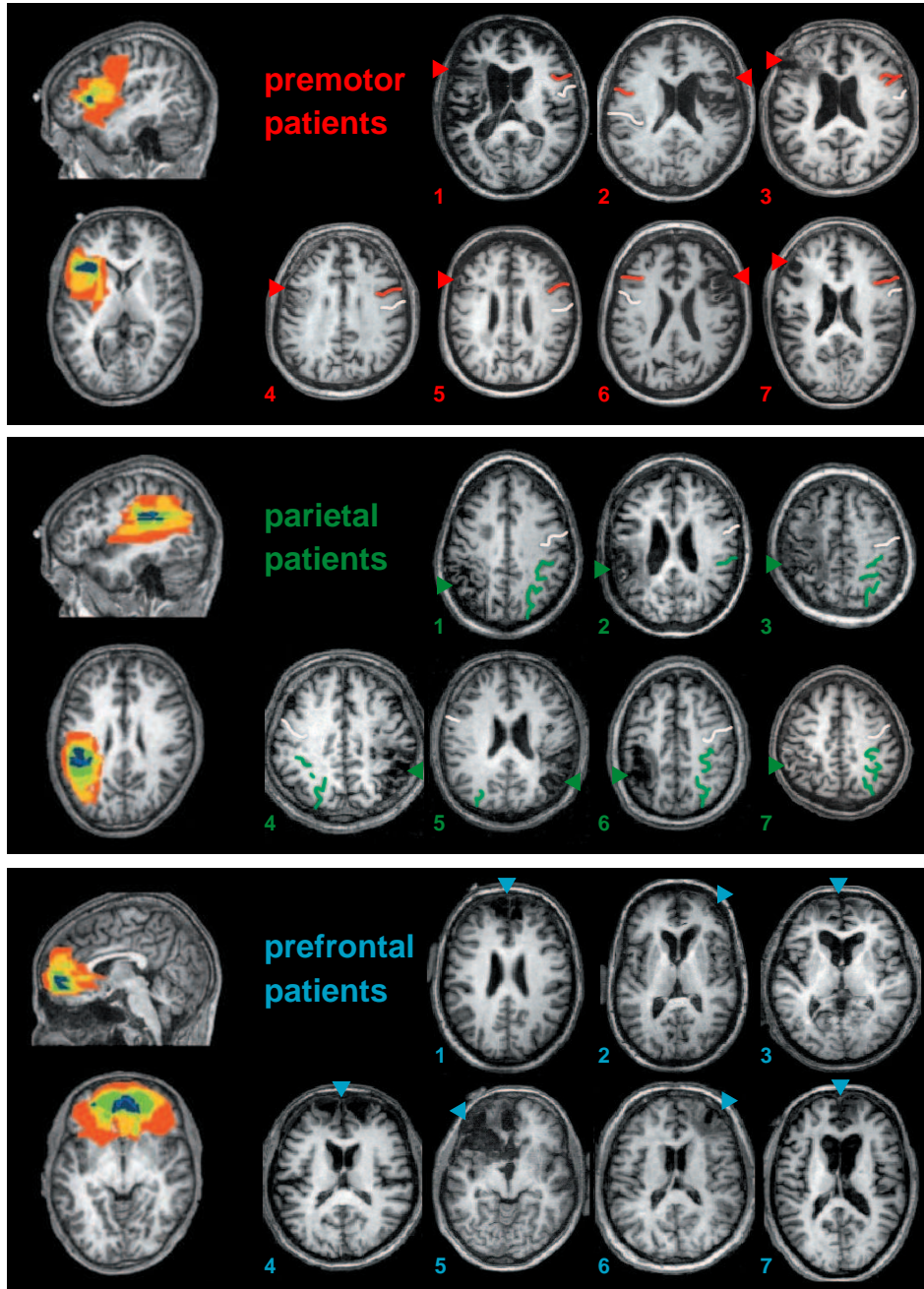


Figure 8.5: Representative axial slices of T1-weighted MRI scans for premotor, parietal, and prefrontal patients investigated in Experiment 12. Lesion sites are indicated by triangles. The following sulci are highlighted in the intact hemisphere for better orientation: central sulcus (white), inferior precentral sulcus (red), and intraparietal sulcus (green). In addition, overlays are shown for each patient group, with red color indicating minimum and blue indicating maximum overlap, respectively.



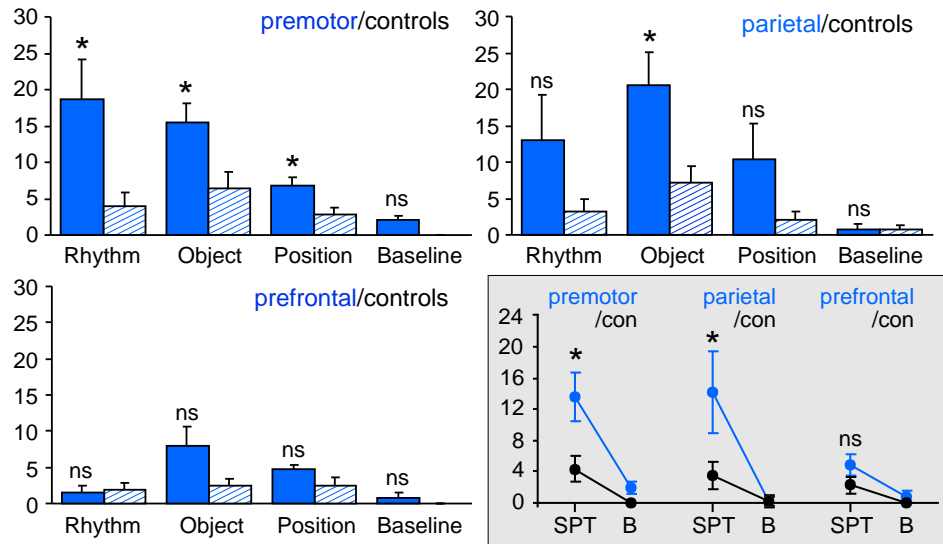


Figure 8.6: Behavioral performance in serial prediction as investigated in patients with ventrolateral premotor, parietal, and prefrontal lesions. Findings indicate that both premotor and parietal (but not prefrontal) lesions lead to significant impairments in the SPT.

## 8.11 Serial prediction in patients

Functional MRI findings indicated that a premotor-parietal network is involved in the perceptual processing of sequential information. Since premotor functions have traditionally been restricted to behaviors that require motor computations, it has sometimes been argued that premotor engagement in sequential processing reflects task-irrelevant co-activations. In order to test this hypothesis, we investigated in Experiment 12 (Schubotz et al., 2004) the performance of patients with either premotor or parietal lesions in the processing of temporal, object-specific and spatial sequences. In the same study, we also tested patients with prefrontal lesions as a clinical control group as well as age- and gender balanced healthy control subjects for each patient group (see Figure 8.5). The level of difficulty in the serial prediction task paradigm was adapted to the neurological patient population. As shown in Figure 8.6, premotor patients as well as parietal patients made significantly more errors than healthy controls in all sequence tasks. In contrast, the prefrontal patients showed no behavioral deficit at all. We took this finding to confirm the significance of lateral premotor cortex, not only of parietal sites, in non-motor attentional functions.

In extension of Experiment 12, we recently conducted a rTMS study (Experiment 13, to be published). Patient studies are one approach to identify or target regional functions from networks activated in fMRI. However, lesions are most often not strictly focal. An alternative approach is to use repetitive Transcranial Magnetic Stimulation (rTMS) in healthy young subjects to induce transient inference within the stimulated brain region. Using a two by two design, repetitive TMS was applied over the right and the left frontal eye field during early and late phases, respectively, in a spatial serial prediction task. Stimulation sites were estimated on the basis of an anatomical MRI scan in combination with a surface marking using liquid-filled pills. Preliminary results indicate that rTMS significantly impairs performance in spatial serial prediction when applied at the beginning of the sequence over the right frontal eye field. Findings will be discussed in view of early and late stages in a serial prediction task, with encoding prevailing in the former and rehearsal or comparison in the latter phase, and with regard to a different significance of the right and the left frontal eye field for the considered task. Results also show that rTMS provides a unique way to investigate issues that are difficult to address with fMRI, especially temporal dynamics and task significance of selected network components.

## 8.12 Summary of findings

*PM is engaged in prospective attention to sensory events.* Activation of the premotor cortex was found to depend solely on the subject's attempt to extract and predict a sequential pattern from the stimulus train, but not on the presence or the factual detectability of a sequential pattern. Hence, the premotor cortex is activated whenever subjects are instructed to predict serial events as compared to a target detection task using the same physical input, and this applies even if the presented sequences are in fact randomized (Schubotz & von Cramon, 2002a, see Figure 8.7, A and B).

Note that this effect does not result from different task demands in the compared conditions. For instance, premotor activation is found when serial prediction is contrasted with an equally difficult serial match-to-sample task (Schubotz & von Cramon, 2002b, see Figure 8.7, C and D). The relevance of a predictive task for PM engagement may also be reflected by the absence of premotor activation in a motion observation task that does not require prediction (Perani et al., 2001). In this respect, our findings fit well with a recent study that investigated the influence of task on premotor activation (Chaminade et al., 2002). Authors find PMv response to manual action observation only if the goal or outcome of said action was to be subsequently imitated, pointing to a final state coding within PMv (see also Umiltà et al., 2001). Correspondingly, the attempt to extract the expected

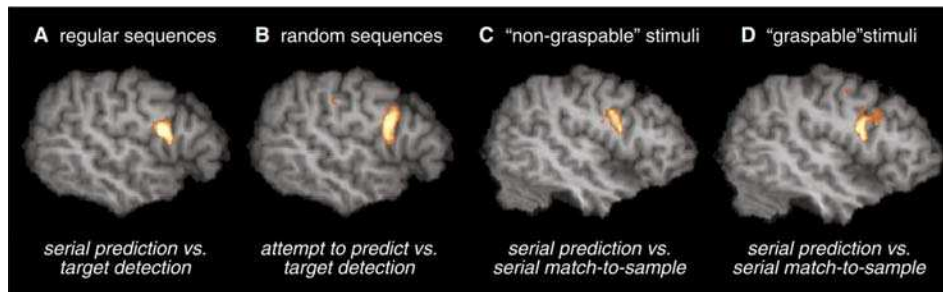


Figure 8.7: *PMv activation in the right hemisphere from two visual serial prediction task (SPT) paradigms (A and B: Schubotz and von Cramon, 2002a; C and D: Schubotz and von Cramon, 2002b). A: standard contrast between SPT performed on regular sequences and a target detection task performed on random sequences. B: Same SPT task as in A, but performed on random sequences. C and D: SPT tasks performed on "non-graspable" and "graspable" abstract stimuli, respectively, each in contrast to an equally difficult serial match-to-sample task. Strikingly similar activations indicate that PMv is reliably activated by prospective attention to sensory events, and that this activation can not be explained by some kind of latent (grasping) action towards stimuli.*

final state from either an observed action or from an abstract visual sequence was found to engage the same PMv areas within both hemispheres (Von Cramon & Schubotz, 2003). We therefore propose the premotor cortex to maintain a short term representation of structured dynamics based on which either sensory prediction or action planning can be performed.

*PM correlates of prospective attention follow a virtual body map.* Premotor activations in serial prediction were found to be distributed according to the to-be-predicted stimulus features, and the overall pattern of these activations strongly suggest that they follow a 'sensory' or 'virtual' body map (Schubotz & von Cramon, 2001a; Schubotz et al., 2003). Within the same experimental setting, we found rhythm prediction to engage inferiormost PMv (face/mouth area), object prediction the (left) middle PMv (hand area), and spatial prediction the dorsalmost PMv (or PMd) (arm area) (see Figure 8.8). This distribution of activation was observed both in visual and in auditory studies. We take these results to confirm that, as proposed in the monkey, PM participates in the representation of the *pragmatic features*, i.e., the potential motor significance, of attended sensory events (Fadiga et al., 2000). It is important to consider that the somatotopical distribution of premotor activation in non-motor tasks does not allow a decision to be made between two alternatives: whether premotor activation reflects 'motor' correlates of sen-

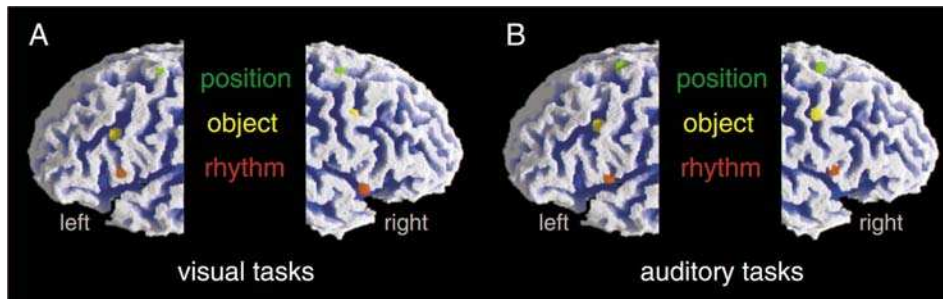


Figure 8.8: *Influence of the attended sensory property on premotor activation (A: Schubotz and von Cramon, 2001a; B: and Schubotz et al., 2003). No matter whether performed on visual (A) or auditory (B) stimuli, the prediction of spatial, object-related and temporal sequences engages three different lateral PM areas. As argued in the corresponding papers, it is suggested that these three activation foci reflect a body-referenced representation of attended events ("habitual pragmatic body map"). Hence, pragmatic features of spatial events are reflected within PM areas for reaching and saccades, those of objects in PM areas for grasping and manipulation, and those of rhythm (or pitch) in PM areas related to vocal production.*

sory events, or rather truly 'sensory' correlates (see Figure 8.9). It is of course possible that premotor neurons that respond to sensory events do not code potential arm, hand and mouth movements, but rather spatial, object and rhythmic or pitch features. Moreover, a 'supramodal' coding is also conceivable in principle. The concept of a 'habitual pragmatic body map' is not intended to exclude one of these alternatives.

*PM is notably flexible with respect to sensory representations.* Premotor activation was found to depend significantly on the stimulus property that subjects were to attend to, but to be independent of the employed stimulus material. Hence, the premotor cortex is activated for instance not only by natural objects, but also by non-natural objects (figures) or non-natural noises. We have found significant premotor activations for any type of abstract visual and auditory stimulus material. In a certain sense, however, one could argue that small geometrical objects are reminiscent of graspable objects. Therefore, we systematically investigated the influences of stimulus features in two fMRI studies, which showed that activation within the premotor cortex did not co-vary with the size (or virtual *graspability*) of presented object stimuli (Schubotz & von Cramon, 2002b). Examples for the stimulus material and results and of the second experiment in

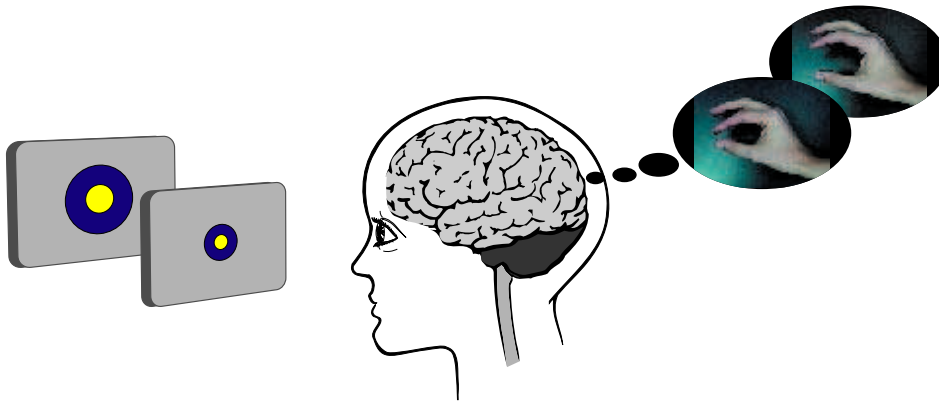


Figure 8.9: *Present fMRI results support the idea that, as proposed in monkey, the lateral premotor cortex participates in the representation of the pragmatic features, i.e., the potential - and habitually most probable - motor significance of attended sensory events.*

this publication are shown in Figure 7.1 and 8.7 (panels C and D), respectively. In addition, findings also indicate that premotor activation can not be attributed to a latent action like grasping, but rather reflects a body-referenced but abstract representation of attended sensory properties. Further evidence for this high level of abstraction comes from a study that compared serial prediction performed either on videotaped manual action or on abstract geometrical object sequences (Von Cramon & Schubotz, 2003), and a study that employed machine-like sounds that were not producible by human voice (Schubotz et al., 2003). We suggest that environmental features do not have to remind us of specific actions or movements to induce premotor activation on a more or less conscious level. Rather, features are represented in a highly fragmented format that allows for instant recombination and very flexible coding of any currently attended environment.

*PM fields show modality preference, but no specialization.* In addition to and independent of property-dependent premotor modulations described so far, sensory modality of attended events appeared to have an influence on premotor activation as well. In particular, inferior PMv and superior PMv are preferentially activated by auditory and visual stimuli, respectively. Moreover, increasing sequential complexity in an auditory and in a visual prediction task was found to co-vary positively with the BOLD signal in these two PMv subregions. At the highest level of complexity, PMd (or the dorsal rim of PMv) was activated independent of modality (Schubotz & von Cramon, 2002c, see Figure 8.10). Note however that in this study, the influence of auditory pitch was compared with visual size

sequences so that both effects of property and effects of modality were concurrently manipulated. We therefore addressed the issue of modality specificity in an auditory and a visual study, each employing serial prediction conditions of temporal, object-related and spatial events (Schubotz & von Cramon, 2001a; Schubotz et al., 2003). In addition to the described property-dependent premotor modulations, visual and auditory serial prediction generally elicited activation within the superior PMv and the inferior PMv, respectively (Figure 8.10). Currently it can not be excluded that superior PMv activation emerges because the processing of object properties is not suppressed in visual sequences, whereas inferior PMv is activated by unsuppressed rhythmic processing in auditory sequences.

*PM reflects a task-relevant process in serial prediction.* In addition to the premotor cortex, its parietal projection sites were co-activated in serial prediction tasks in most studies. As we know from research in the monkey, premotor and parietal areas form multiple parallel loops for sensorimotor transformation (Rizzolatti et al., 1998). While functional-anatomical properties of the premotor cortex have been focused in the present work, of course parietal projection sites substantially contribute to considered functions. A crucial question is therefore whether premotor or parietal areas alone may account for performance in serial prediction. Using fMRI, it is impossible to test an area's task-relevance: It is principally possible that a significant BOLD response reflects a (redundant) behavioral strategy, and it is also possible that activation within actually task-relevant areas fail to reach statistical threshold. In light of these methodological limitations, we conducted a patient study, testing the hypothesis that premotor lesion do not affect performance in a serial prediction task. As a result, this hypothesis could be rejected. Following our expectations, compared to parietal and prefrontal patients, premotor patients were most significantly impaired in all three tested types of visual serial prediction (Schubotz et al., 2004, see Figure 8.6).

### 8.13 Premotor cortex as a forward model

Considering the functional properties of dorsal and ventral premotor cortex that have been outlined so far, findings from the SPT paradigm indicate a representation of sensory events in human lateral premotor cortex that is referenced to the body. Thus, PMd (or the dorsal rim of PMv) is engaged in movements of foot and arm and in spatial information processing, whereas (inferior) PMv is engaged in movements of fingers, mouth and vocal tract and in object information processing. Within this latter compartment, the inferiormost portion of PMv (BA 6/44) is engaged in the processing of temporal (rhythm) information and pitch, what has, as far as we know, not yet been investigated in the monkey. The present account integrates both effector-specific modulations as well as information-specific

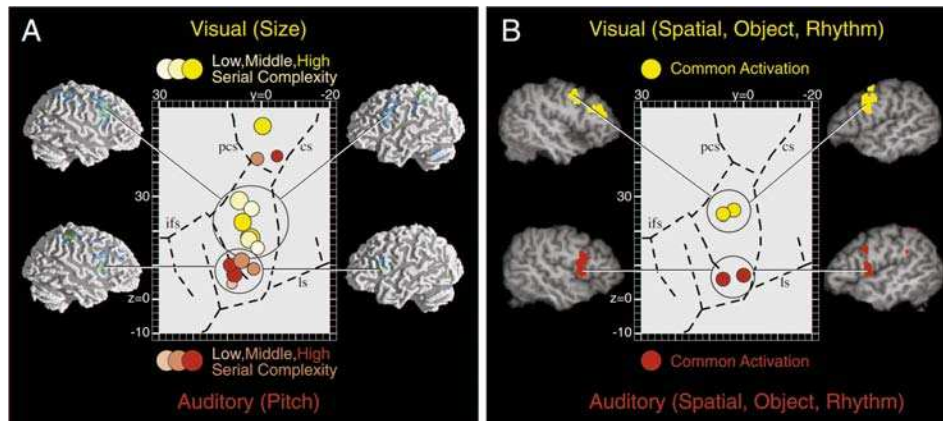


Figure 8.10: Influence of the sensory input modality on premotor activation (A: Schubotz and von Cramon, 2002b; B: Schubotz and von Cramon, 2001a, and Schubotz et al., 2003). Between-studies and within study comparisons show that, in addition to effects of the attended stimulus property, visual stimuli generally engage superior PMv, whereas auditory ones rather engage inferior PMv. Abbreviations: cs central sulcus, ifs inferior frontal sulcus, ls lateral sulcus, pcs precentral sulcus.

modulations of premotor activations. It supports the view that spatial attention is a consequence of an activation of brain areas which are also involved in the transformation of spatial information into action (*premotor theory of attention*, Rizzolatti et al., 1987b). Likewise, however, object attention and attention related to speech-related properties like pitch (frequency) and rhythm may be a consequence of an activation of brain areas (including PM) which are also involved in the transformation of object (pitch, rhythm) information into action.

As reported effects become especially evident when the *prediction* of environmental *dynamics* is required, rather than merely *attending* to environmental *static* features, it could be suggested that the premotor cortex serves to establish an internal forward model of what the organism expects to experience in short term (see Figure 8.11, Schubotz & von Cramon, in press). To this end, multiple premotor-parietal loops, each linking both heteromodal and unimodal representations, may be exploited by the preSMA and prefrontal areas for perception, action, and imageries; visual, auditory, or tactile predictions or imageries might be generated by efferent signals to and feedbacks from the corresponding unimodal association cortices, with current internal and external requirements determining which feedback becomes causally effective. Two behavioral implementations of PM as such

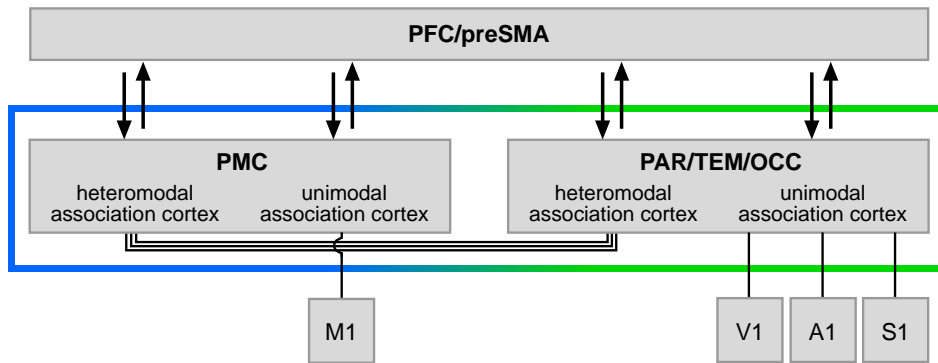


Figure 8.11: *Lateral premotor areas can be conceived of as functioning as an internal forward model (Schubotz and von Cramon, in press).*

a forward model can be considered. Firstly, being prepared for the near future enables us to react quickly and appropriately. Following the medial-lateral dichotomy outlined above, activation within lateral premotor sites may correspond to the effector that is habitually *guided* by the attended sensory signal. Alternatively, however, activation within lateral premotor cortex may correspond to the effector that habitually *effects* the attended sensory signal. This account of the premotor cortex goes beyond the classic term of a passive action-perception adaptation module. It considers the premotor cortex as that part of a network that represents upcoming events, no matter if these are caused by an external source or by the subject/animal itself. This account may be conceived of as neurofunctional counterpart of a psychological model that considers actions to be planned in terms of intended sensory effects, the *Theory of Event Coding* (Hommel et al., 2001). Together, findings point to a dual premotor function, one related to motor output, the other to attentional and receptive functions, both referenced to a body map. We especially propose that dorsal-ventral differences of attentional non-motor tasks that engage premotor areas can be explained by their representation according to a habitual pragmatic body map. In contrast to the historic view, but in accordance to recent findings in the monkey, imaging data indicate that the premotor cortex may be involved in a variety of behaviors, with motor execution being merely the tip of the iceberg. In light of research in the monkey, imaging studies can especially help to further elucidate how cognitive abilities may have evolved from motor functions and structures.





## Chapter 9

# Outlook

Presented imaging findings clearly indicate that premotor functions exceed the classical motor concept. Together with animal findings they persuade us to reconsider what we thought to know about the frontal agranular "motor" isocortex, which today manifests as a multi-purpose and multi-component bridge between perception and action: Action goals, provided by the external environment and suggested by internal drives, are specified in parameters that can be directly passed to the motor effectors, and finally reenter the perception-action circle. However, motor output may be the only visible, but is not the only outcome of the computations that this cortical network is designed for. Rather, a variety of highly specialized premotor neurons appear to mediate different aspects of voluntary action and attention, though we are still ignorant about how they interact to do so. From the current perspective it appears likely that the premotor system, rather than being transiently engaged during the preparation of voluntary action, provides a continuous stream of emerging options for actions, most of which vanishing in favor of the finally chosen one.

Methodologically, the last years have clearly shown that the reliability of human imaging findings is enhanced when they are attuned to the data from other imaging laboratories and also to animal findings. Only careful inspection of convergences and divergences between imaging studies can stepwise improve our understanding of the basic neurological and computational components that make up our behavioral abilities. On the other side, animal findings can inspire new research issues in the human and help to develop refined experimental paradigms. Many strands of imaging research, including the present work, have successfully demonstrated that it does make sense to re-test effects that are found in monkeys by appropriately modified imaging paradigms in humans. However, it appears for several reasons that human and monkey data can be integrated, if possible, only in the long run. One major obstacle is that we are still largely ignorant about

functional and anatomical homologies between species. To take one example, we do not know how cortico-cortical networks have evolved from monkey to homo sapiens. Although the neuroanatomical architectures of both species may be by and large comparable, quantities and qualities of projections might have drastically altered. This is for instance implicated by the divergence of the behavioral repertoire, as particularly evident in movement control. Moreover, a fundamental gap remains between the microscopic scale of single cell studies and the mesoscopic scale of current imaging techniques. Recently established fMRI methods in monkeys may therefore become more popular in future not only because of their ethical superiority, but also because they allow to use exactly the same experimental and methodological approach in different species. Certainly, this comparability comes at the expense of giving up the highest possible spatial resolution that can be obtained in monkey research. Finally, one should not overvalue the idea of a direct reciprocal experimental comparison between monkey and human. One has to keep in mind that most experimental tasks that are acquired with ease by a human subject have to be excessively trained, even over months, to achieve a comparable performance in monkeys.

The common denominator of premotor functions that emerges especially from the presented fMRI work is the representation or processing of sequential information, independent from overt or covert motor functions. Investigated on a fairly abstract level in case of the serial prediction task paradigm, sequencing is yet a core component in everyday life behaviors such as action, planning, language, music, mental arithmetic, or logical reasoning. Across these applications, it plays a role not only in the domain of motor output or stepwise sensorimotor integration, but also in more domains like causal linkages (which actually coincide with *temporal* linkages, but not vice versa). These different implementations of sequencing mechanisms, and their potential transfer between primarily distinct behavioral domains, remain to be systematically investigated both behaviorally and neurophysiologically.

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# Abbreviations

CMA	cingulate motor area
CO	cytochrome oxidase
F5c	F5 of the cortical convexity, F5 convexity
FEF	frontal eye field, area 8
FV	frontal ventral area
HRP	horseradish peroxidase
ICMS	intracortical microstimulation
IPL	inferior parietal lobule
LIP	lateral intraparietal area, part of area 7
MI	primary motor cortex
MIP	medial intraparietal area, part of area 5
MST	medial superior temporal area
OMD	dorsal oculomotor area
PE	part of parietal area 5
PEc	caudal part of PE
PEci	cingulate part of PE
PEip	anterior part of parietal area PEa

PFG	part of parietal area 7
PG	parietal area 7a
PGm	mesial part of parietal area 7
PM	premotor cortex, area 6
PMd	dorsal premotor cortex
PMv	ventral premotor cortex
PZ	polysensory zone
RA	receptor autoradiography, radio-ligand autoradiography
rTMS	repetitive Transcranial Magnetic Stimulation
SEF	supplementary eye field
SI	primary somatosensory cortex
SII	secondary somatosensory cortex
SMA	supplementary motor area
SPL	superior parietal lobule
SPT	Serial Prediction Task
STG	superior temporal gyrus
V6A	part of visual area 19
VApC	nucleus ventralis anterior pars parvocellularis (area X)
VIP	ventral intraparietal area, part of areas 5 and 7
Vlo	nucleus ventralis lateralis pars oralis

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