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CHAPTER 4

Principles of corticospinal system organization and function

Paul D. Cheney*, Abderraouf Belhaj-Saïf and Marie-Héléne Boudrias

Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS 66160, USA

4.1. Introduction

Throughout vertebrate phylogeny, the corticospinal system has enlarged in size and importance with expansion of the cerebral cortex and with development of skilled use of the extremities. Comprehensive and detailed monographs covering various aspects of corticospinal structure, function, and related issues have been published (Phillips and Porter, 1977; Porter and Lemon, 1993). The goal of this chapter will be to present a set of principles that represent an attempt to summarize the current state of knowledge about the organization and function of the corticospinal system in primates. In the spirit of this goal, the chapter has been organized around 20 sections with subheadings each of which states a principle to be discussed ("top twenty list"). While emphasis will be placed on what is known about the corticospinal system, the limitations in our understanding and potential directions of interest for future investigation will also be noted. No systematic attempt will be made to consider development of the corticospinal system, species differences or disease conditions because these topics are the subject of other chapters.

4.2. Functional components of the cortical efferent system

1. *The functional roles of cortical output neurons fall into four broad categories: (1) movement execution-related, (2) reflex modulation-related, (3) sensory modulation-related, and (4) internal motor program-related.*

Descending output to subcortical structures from the frontal and parietal areas of cerebral cortex includes projections to the thalamus, striatum, brainstem nuclei (corticobulbar or corticofugal) and spinal cord (Fig. 1). These cortical efferents can be categorized into four types based on their primary functional role: (1) movement execution-related, (2) reflex modulation-related, (3) sensory modulation-related, and (4) internal motor program-related. Corticospinal (and corticobulbar) neurons are represented in each of these categories.

Movement execution-related neurons include corticospinal and corticobulbar neurons whose primary role is the excitation and inhibition of motoneurons either directly or indirectly through brainstem descending systems, propriospinal neurons, and spinal cord interneurons. Corticobulbar neurons, in this case, are upper motoneurons terminating in brainstem motor nuclei supplying muscles of the face, head, jaw and tongue. Corticospinal and corticobulbar neurons that terminate monosynaptically on motoneurons are referred to as corticomotoneuronal cells. This linkage can be demonstrated anatomically using light or electron microscopy (Ralston et al., 1988), electrophysiologically with intracellular recording of EPSPs or IPSPs (Preston and Whitlock, 1961; Landgren et al., 1962a,b) or by measuring the timing of volleys in the ventral roots (Bernhard and Bohm, 1954).

Another category of corticobulbar neuron influences motoneurons indirectly through actions on brainstem descending systems. These brainstem neurons are involved in movement execution and include tectospinal neurons located in the superior colliculus, interstitiospinal neurons located in the interstitial nucleus of Cajal, rubrospinal neurons located in the red nucleus and reticulospinal neurons located in the nucleus reticularis tegmenti pontis and the medullary reticular formation. Also, neurons in the lateral vestibular nucleus (Dieters nucleus) are

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*Correspondence to: Dr. Paul D. Cheney, Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS 66160-7430, USA.

E-mail address: pcheney@kumc.edu (P.D. Cheney).
Tel.: +1-913-588-7400; fax: +1-913-588-7430.

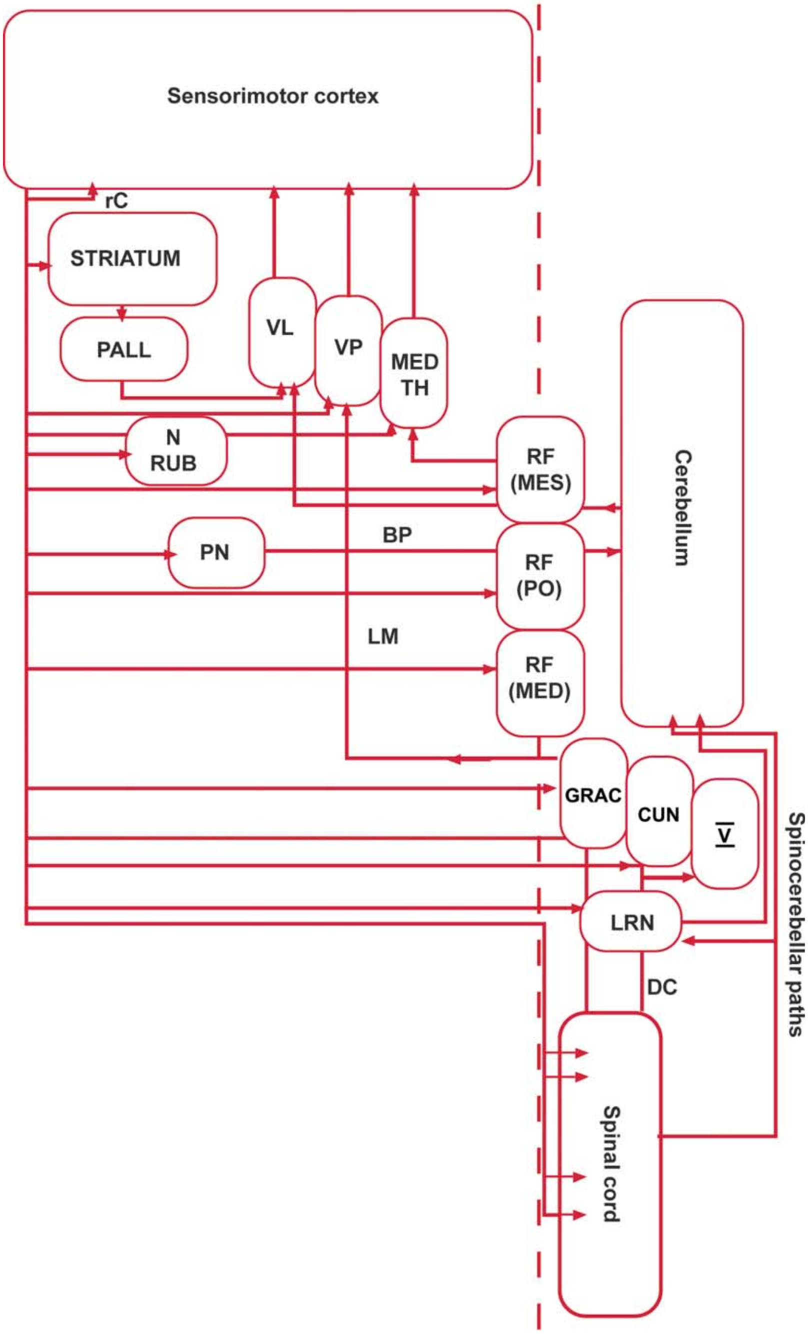

Fig. 1. Schematic representation of the connections of the pyramidal tract. Collaterals of pyramidal neurons occur within the cerebral cortex (rC is recurrent collaterals). Other targets of pyramidal axon collaterals include the basal ganglia (striatum), the specific (VP) and unspecific (MED) thalamic nuclei, the red nucleus (N RUB), the pontine nuclei (PN), the mesencephalic (MES), pontine (PO), and the medullary (MED) reticular formation (RF), the dorsal column and trigeminal nuclei (GRAC, CUN, V), and the LRN. Collaterals also distribute at various spinal levels. Pyramidal tract collaterals may function as parts of internal feedback loops. The main internal feedback loops to the cerebral cortex are the lemniscal system (LM) and specific thalamic nuclei (VP), the cerebellum-ventrolateral nucleus of the thalamus (VL), and the pallidum (PALL) – VL system. Dotted line indicates midline. From Wiesendanger (1981) as reproduced in Porter and Lemon (1993).

known to have powerful excitatory connections with motoneurons, particularly with those of extensor muscles. While it has been a commonly held view that vestibulospinal neurons receive no cortical input (Brodal, 1981), more recent studies in the rat have shown that vestibulospinal neurons can be activated easily by stimulation of cortical areas controlling extensor muscles (Fukushima et al., 1984; Licata et al., 1990; Fukushima, 1997).

Another non-monosynaptic route by which corticospinal neurons can influence motoneurons is through the propriospinal system. Propriospinal neurons are located in the upper cervical segments. Their axons traverse several spinal segments making synapses with motoneurons. A debate has emerged recently about the involvement of the propriospinal neurons in descending corticospinal control of motoneurons in primates. Alstermark and Ohlson (1999) showed that this system is prominent in cats and is critically important for visually guided reaching movements. In old world primates on the other hand, Lemon et al. (2004) found little evidence for involvement of propriospinal neurons in corticospinal EPSPs to forelimb motoneurons in rhesus macaques (Nakajima et al., 2000). In the squirrel monkey, a new world primate, the contribution of propriospinal neurons to EPSPs mediated by cortical stimulation was significant although still much less than in the cat. Alstermark and Isa (2002) have challenged this result arguing that the absence of evidence of propriospinal neuron involvement in the work of Lemon et al. was due to the suppressive effects of anesthesia. By giving strychnine to block inhibition, they found evidence of EPSPs mediated by propriospinal neurons (Alstermark et al., 1999). However, in awake or lightly sedated macaque monkeys, Lemon and colleagues were unable to find evidence of non-monosynaptic corticospinal excitation of upper limb single motor units in response to stimulation of the pyramidal tract so the controversy continues (Kirkwood et al., 2002; Olivier et al., 2001; Lemon et al., 2004).

Sensory-related cortical efferent neurons arise predominantly from primary somatosensory (S1) cortex and make synaptic connections with neurons of ascending sensory systems at various levels of the neuraxis. These neurons are involved in modulating the flow of somatosensory information from the periphery to the cortex. Two targets of such cortical modulation are the dorsal column nuclei and the dorsal horn of the spinal cord (Fetz, 1968). Tracer injection studies labeling S1 corticospinal neurons have demonstrated terminations predominately in the dorsal horn of the spinal cord (Ralston and Ralston, 1985). Using stimulus-triggered averaging of EMG activity, Widener and Cheney (1997) showed that S1 output produces largely inhibitory effects on motoneurons. The exception was area 3a, which produced more excitatory effects including postspike facilitation (PSpF) of EMG activity from single cells. Reflex-related cortical efferent neurons influence reflex pathways in the spinal cord and brainstem. For example, it is well known that corticospinal neurons make synaptic connections with Ia inhibitory interneurons (Jankowska et al., 1976) and with interneurons in pathways from Golgi tendon organ afferents and flexor reflex afferents (Rudomin et al., 1983). Descending corticospinal activity has also been shown to suppress primary afferent depolarization (PAD or presynaptic inhibition) of Ia afferents terminals by group I afferents or vestibulospinal volleys (Rudomin, 1990; Meunier and Pierrot-Deseilligny, 1998). This suppression might occur through inhibitory effects on the inhibitory interneurons involved in mediating PAD. In contrast, Ib afferent fibers receive direct PAD from corticospinal and other descending systems. Little is known about presynaptic inhibition of the corticospinal fibers themselves. It has been suggested based on conditioning of cortical H-reflexes in ankle muscles in humans that that corticospinal terminals lack presynaptic control from muscle afferents (Nielsen and Petersen, 1994). Evidence also exists for corticospinal depression of recurrent inhibition of motoneurons from Renshaw cells (Mazzocchio et al., 1994). Thus the cortex is able to exert a variety of modulatory controls over major spinal reflex and interneuronal pathways.

Finally, a large number of cortical efferent neurons project to the thalamus, striatum, pons and lateral reticular nucleus (LRN) and do not directly influence either motoneurons or sensory input signals. These neurons are involved in various aspects of generating an internal motor program for execution by the corticomotoneuronal system. In this sense, these cortical neurons are involved in internal signal processing in support of motor program formation and updating. Motor program formation and updating must include a wide array of different processes, including movement trajectory formation specified in terms of signals compatible with the peripheral motor apparatus. Part of this includes coordinate transformations in which input signals from sensory systems or from memory are converted into motoneuron/muscle-specific signals appropriate for producing the desired movement trajectory. This is an aspect of cortical function that seems to involve a number of frontal and parietal cortical areas as well as the cerebellum, but is not well understood and represents one of the major challenges in the field.

2. *Corticospinal neurons have a minimal monosynaptic excitatory linkage with motoneurons of agonist muscles and a minimal disynaptic inhibitory linkage with motoneurons of antagonist muscles.*

The synaptic linkage between corticospinal neurons and motoneurons has long been a topic of great interest and importance. Early intracellular recording studies and more recent ones have demonstrated that in primates, the minimum synaptic linkage from M1 corticospinal neurons to motoneurons is monosynaptic (Phillips and Porter, 1977; Porter and Lemon, 1993; Lemon et al., 2004). In new world primates and other species that have been studied extensively, such as the cat and rat, a monosynaptic linkage is minimal or nonexistent (Yang and Lemon, 2003; Alstermark et al., 2004). Lemon et al. have argued that the development of monosynaptic connections correlates with skilled use of the hand and ability to perform individual finger movements. In a recent study, 88% of motoneurons supplying muscles of the hand and fingers received EPSPs from M1 (Lemon et al., 2002; Maier et al., 2002). The corticospinal EPSPs elicited in 19% of these motoneurons were mediated by monosynaptic connections. In another study of 79 forearm and hand motoneurons tested, 43% showed EPSPs in response to ICMS at 20 μA from a single site in M1 (Fritz et al., 1985). Cortical EPSPs are larger and more frequent in motoneurons of distal muscles than those of proximal muscles. In their classic work on this topic using large surface anodal stimulation applied to the cortex, Phillips and Porter (1964) showed that about half of the motoneurons supplying proximal muscles (e.g. triceps brachii) received no detectable monosynaptic excitation. In comparison, all motoneurons supplying the intrinsic hand muscles received monosynaptic EPSPs. Of course, the fact that a particular linkage is less than monosynaptic does not mean that it is necessarily less important in the execution of movement or that it would necessarily have less ability to fractionate movements at different joints.

Disynaptic IPSPs have also been demonstrated in motoneurons from corticospinal stimulation (Phillips and Porter, 1964). These IPSPs are probably largely mediated by Ia reciprocal inhibitory interneurons. In a set of elegant studies, Jankowska et al. identified and localized Ia inhibitory interneurons and showed that these interneurons receive convergent input from several sources including motor cortex (Jankowska and Roberts, 1972; Jankowska and Tanaka, 1974). Consistent with cortical excitation of Ia inhibitory interneurons, Kasser and Cheney (1985) demonstrated postspike suppression (PSpS) in spike-triggered averages of EMG activity of antagonist muscles. In nearly all these cases, the neurons also facilitated one or more agonist muscles. Agonist muscles are ones that show coactivation with the cell during various motor tasks. Existing evidence does not support the existence of cortical cells that only inhibit motoneurons without also producing facilitation of other motoneurons.

A final issue is corticospinal input to static and dynamic gamma (fusimotor) motoneurons supplying intrafusal muscle fibers of the muscle spindle. Cortical stimulation evokes monosynaptic EPSPs in gamma motoneurons and presumably both static and dynamic gammas but the gammas have not been identified as to type (Clough et al., 1971; Phillips and Porter, 1977). These direct connections to gamma motoneurons are presumably involved in producing coactivation of alpha and gamma motoneurons associated with many types of voluntary movements. It is not known whether the corticospinal input to gamma motoneurons is independent of that to alpha motoneurons or if it is partly or entirely from collaterals of corticospinal neurons supplying alpha motoneurons. There is evidence for dissociation of activity in alpha and gamma motoneurons under some conditions (Cody et al., 1975; Schieber and Thach, 1980; Hulliger et al., 1989; Taylor et al., 2000). Assuming corticospinal neurons are responsible for this dissociation, alpha and gamma motoneurons must be supplied, at least in part, by separate corticospinal neurons. Independent control of static and dynamic gammas would require a further level of specificity in the distribution of terminations from corticospinal and other descending systems.

4.3. Distribution of corticospinal neurons

3. *Corticospinal neurons are distributed over broad regions of fronto-parietal cortex including six premotor areas in the frontal lobe.*

Our understanding of the distribution of corticospinal neurons and cortical motor areas has changed dramatically in recent years. Injection of retrograde tracers in the spinal cord of macaque monkeys has revealed that corticospinal neurons whose axons project to or near motoneuron pools in the spinal cord are not confined to primary motor cortex but, in fact, arise from multiple, separable regions within the frontal lobe of primates (Dum and Strick, 1991, 1996; He et al., 1993, 1995; Galea and Darian-Smith, 1994; Picard and Strick, 1996). Seven distinct forelimb motor representations within the frontal lobe have now been identified (Fig. 2), including primary motor cortex (M1), supplementary motor area (SMA); dorsal, ventral and rostral cingulate motor areas (CMAd, CMAv, and CMAr) on the medial aspect of the hemisphere; and dorsal and ventral premotor areas (PMd and PMv) on the lateral aspect of the hemisphere (Dum and Strick, 1991, 1996; He et al., 1993, 1995). Excluding primary motor cortex (M1), this leaves six areas that are considered "premotor" cortical areas because they project both to the spinal cord and to primary motor cortex (Dum and Strick, 1991). Table 1 is a summary of the number of corticospinal neurons contained in these areas in comparison to M1.

Support for these areas as distinct motor output representations of the forelimb is based not only on the distribution of corticospinal neurons, but also on cytoarchitectonics and patterns of projection to and from primary motor cortex, parietal cortex and thalamus (Gentilucci et al., 1988; Dum and Strick, 1991, 1996; Kurata, 1991; Luppino et al., 1991; He et al., 1993; Galea and Darian-Smith, 1994; Zilles et al., 1995). Fig. 2 is taken from the work of Strick et al. (He et al., 1993; Dum and Strick, 1996) and summarizes their findings on the distribution of corticospinal neurons in the frontal lobe. It is important to note that, unlike corticospinal neurons in primary somatosensory and parietal cortex, which terminate largely in the spinal cord dorsal horn (Fetz, 1968) and dorsal column nuclei (Bentivoglio and Rustioni, 1986), frontal lobe corticospinal neurons make terminations in the ventral horn and intermediate zone of the spinal cord. In some cases, the density of termination in the ventral horn from premotor area corticospinal neurons is similar to that from primary motor cortex (Dum and Strick, 1996). The spinal cord terminations of cortical premotor areas will be discussed more fully in later sections.

Galea and Darian-Smith (1994) measured the number of corticospinal neurons in different corticospinal output zones of the frontal lobe. They estimated that 70% of the total contralateral corticospinal projection originates from frontal and cingulate cortex. Of these neurons, 58% originate from primary motor cortex, 22% from SMA, 14% from cingulate motor areas (CMAs) and 4% from the arcuate premotor areas on the lateral surface of the hemisphere. These numbers are in general agreement with those of Strick et al. (Table 1). Dum and Strick (1991) reported that the total number of corticospinal neurons in the arm representation of the premotor areas equals or exceeds the total number in the arm representation of primary motor cortex. Also, the premotor cortical areas collectively constitute more than 60% of the frontal lobe with projections to the spinal cord. The premotor areas differ in the distribution of their projections to motoneurons of distal and proximal forelimb muscles (Table 1). Projections to distal muscles were identified based on injections of horseradish peroxidase (HRP) into upper cervical spinal cord segments (C2–C4); proximal muscles were identified by injections of HRP into lower cervical segments (C7–T1). Hindlimb corticospinal neurons were identified by HRP injections into lumbar segments (L6–S1).

4. *The set of corticospinal neurons terminating on a single alpha motoneuron (motor unit) is termed a "cortical colony". Cortical colonies have broadly overlapping territories in the cortex.*

Andersen et al. (1975) used anodal electrical stimulation of the cortical surface to map the cortical territory from which EPSPs could be elicited in single hindlimb alpha motoneurons defining the cortical representation of single motor units. This method provides a measure of the degree of convergence from multiple cortical neurons to single motoneurons. It is noteworthy that these territories are relatively large (5–12 mm^2). The resulting maps provide clear evidence that the cortical territories representing single motoneurons (motor units), even those belonging to different muscles, are extensively overlapping. This can be conceptualized by defining the collection of all corticospinal cells that project to a single motoneuron as the cortical colony for that

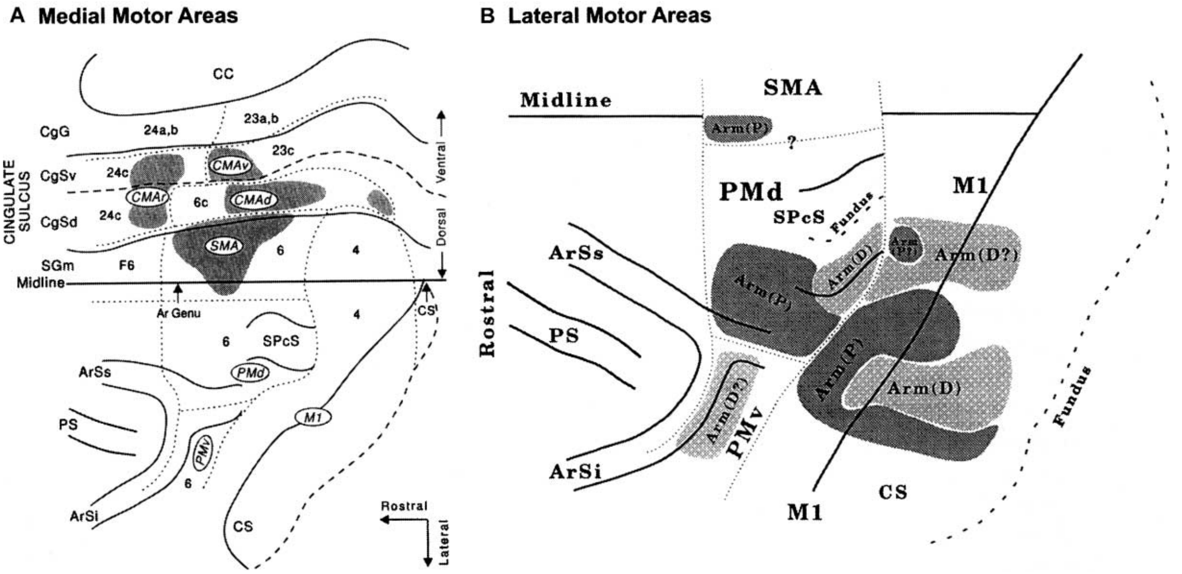

Fig. 2. (A) Origin of corticospinal projections from the motor areas on the medial wall of the hemisphere. This reconstruction of the frontal lobe of a macaque brain indicates the origin of corticospinal neurons (shaded regions) that project to the cervical segments of the spinal cord. In this view, the medial wall is unfolded and reflected upward to reveal the cingulate sulcus. The anterior bank of the central sulcus is also unfolded. A dashed line marks the fundus of each unfolded sulcus. The centers of the different cortical motor areas are designated by the circled letters. The boundaries between the motor areas and cytoarchitectonic areas (identified by numbers) are denoted with dotted lines. ArGenu (with arrow), level of the genu of the arcuate sulcus; ArSi, inferior limb of the arcuate sulcus; ArSs, superior limb of the arcuate sulcus; CC, corpus callosum; CgG, cingulate gyrus; CgSd, dorsal bank of the cingulate sulcus; CgSv, ventral bank of the cingulate sulcus; CMAd, cingulate motor area on the dorsal bank of the cingulate sulcus; CMAr, rostral cingulate motor area; CMAv, cingulate motor area on the ventral bank of the cingulate sulcus; CS, central sulcus; M1, primary motor cortex; PMd, dorsal premotor area; PMv, ventral premotor area; PS, principal sulcus; SGm, medial portion of the superior frontal gyrus; SPcS, superior precentral sulcus; SMA, supplementary motor area (from Dum and Strick (1996)). (B) Proximal and distal representation in the arm areas of the primary motor cortex and the premotor areas on the lateral surface of the hemisphere. This map is based on the peaks in the distribution of corticospinal neurons labeled following tracer injections into lower cervical and upper cervical segments. M1, primary motor cortex; PMd, dorsal premotor area; PMv, ventral premotor area; SMA, supplementary motor area; ArSs, superior arcuate sulcus; ArSi, inferior arcuate sulcus (modified from He et al. (1993) and Dum and Strick (1996)).

motoneuron. Although the territories of individual cortical colonies show extensive overlap, the best point on the cortex eliciting the largest EPSP is usually slightly displaced for each motoneuron or muscle. This probably reflects the fact that the geometric centers of the colonies are not exactly superimposable, and the points containing the greatest density of corticospinal neurons projecting to different motoneurons or muscles are also displaced from each other. In some cases, multiple noncontiguous best points were identified (Andersen et al., 1975).

5. *The cortical territories representing individual muscles and influencing movements about individual joints are broadly overlapping.*

This has been a topic of great interest going back many decades in the study of motor cortex organization. The orderly representation of sensory input to area 3b of primary somatosensory cortex in primates exemplified by the separate but adjacent cortical territories representing the digits of the hand in correct anatomical order (Nelson et al., 1980) is not matched by a parallel organization in primary motor cortex, even though the basic areal features of somatotopy are similar from S1 to M1 cortex. Rather, most studies of M1 organization have demonstrated extensive overlap of cortical territories representing movements about individual joints or individual muscles. The cortical territories representing movements about individual joints have been studied by

Table 1

Properties of cortical premotor areas in relation to primary motor cortex (M1).

Cortical area	MI (F1)	SMA (F3,6aβ)	CMAd (6c,24d)	CMAv (23c,24d)	CMAr (24c)	PMd (F2,6aα)	PMv (F4–F5)
Total number of CS neurons							
Forelimb distal (LC[a])	10,000	2400	800	1200	1200	3400	1000
Forelimb prox. (UC[a])	10,000	2800	2600	1000	800	3200	160
Hindlimb (L6-S1)	10,800	2800	2200	1400	200	2600	0
Percentage of high-density bins (cervical, upper 10%)	53	19	15	7	<1	5	<1
Cortical area occupied by forelimb CS neurons (mm^2)	84	44	22	14	24	20	18
Percentage of total frontal lobe CS projection (frontal lobe = 70% of total)	51	13	9	6	4	15	2
Density of CS neurons (median, cells per mm^2)	300	300	300	300	200	300	200
Electrical excitability (estimated average ICMS threshold, μA)	10	20	30	30	35	60	40
Functional activity							
Move execution	+++++	+++	–	++++	++	+++	+++
Set related	++	+++	–	++	++++	++++	++
Signal related	+	++	–	–	–	+	+++
Special functional role	Move execution	Self-initiated movement, sequence, bilateral move	Movement sequence from memory	–	Reward-based motor selection	Sensory-guided movement	Visual grasp, imitation (F5)
Directional tuning	Y	Y	–	–	–	Y	–

Numbers of corticospinal neurons based on data from Dum and Strick (1991) and He et al. (1993, 1995). Reproduced from Cheney et al. (2000); PMv = APA, PMd = SPcS, CMAv = CMAc; – not tested.

[a] lc stands for lower cervical and uc for upper cervical.

applying electrical stimulation to either the cortical surface or by using intracranial microstimulation (ICMS) to produce more restricted activation of cortical output zones (Phillips and Porter, 1977; Donoghue et al., 1992; Porter and Lemon, 1993; Park et al., 2001; Schieber, 2001; Cheney, 2002). ICMS is generally applied as a short train of high-frequency biphasic stimuli (10 pulses at 330 Hz). The results have consistently yielded single or, in some cases, multiple noncontiguous best points for producing movements at a particular joint but the cortical territories from which movement can be evoked are broadly overlapping, particularly for adjacent joints of the same body part.

This type of organization was confirmed by recording the activity of M1 neurons in monkeys trained to move individual digits in isolation (Schieber and Hibbard, 1993). Maps of the locations of neurons whose activity was engaged for movements of each digit show almost complete overlap (Fig. 3).

Fig. 3. Distributed activation in MI during finger movements. (A) Colored spheres each represent a single neuron recorded in the left hemisphere MI as a monkey performed individuated movements (flexion or extension} of each right-hand digit and of the right wrist. Each neuron was consistently related to at least one movement, although most neurons were related to multiple different finger and/or wrist movements. The sphere representing each neuron is centered at the location of the recorded neuron in the anterior bank of the central sulcus, with the hemispheric surface *above*, white matter *below*, lateral to the viewer's *right* and medial to the *left*. Each sphere is sized according to its greatest change in discharge frequency during any of the movements; the white spheres at *left* constitute a scale from 0 to 200 spikes per second, with centers 1 mm apart. Each sphere representing a neuron is colored according to the movement for which that neuron's greatest discharge occurred: thumb, red; index finger, orange; middle, yellow; ring, green; little, blue; wrist, violet. Neurons best-related to movements of each digit or the wrist were intermingled throughout the same cortical territory. (B) Centroids of discharge frequency changes calculated for each flexion movement and each extension movement are shown in the same coordinate system as in (A) with the scale of white spheres as a visual anchor. Rather than shifting progressively across the field of active cortex for thumb through little finger and wrist movements, these centroids are all clustered together in the center of the field, with only a slight shift for movements of different digits or the wrist, reflecting the extensive overlap of the representations of different movements (From Schieber (2001)).

6. *Individual corticospinal neurons generally influence (facilitate or inhibit) motoneurons of multiple muscles termed the cell's muscle field. The muscle fields of corticospinal neurons represent basic functional muscle synergies underlying coordinated movements.*

From a design standpoint, the most anatomically simple organization of output from M1 might be a mosaic organization in which each muscle would have a unique piece of cortical tissue devoted to its control. Individual corticospinal neurons in each piece of tissue would have their synaptic terminations confined to motoneurons belonging to that muscle. It is now clear that this is not the way corticospinal neurons are organized. Not only is there no mosaic organization, but also in addition, the terminations of individual corticospinal neurons typically branch to supply motoneurons of multiple muscles. Such axonal branching with terminations in multiple motoneuron pools is itself inherently inconsistent with a mosaic organization in which individual muscles are represented as distinct pieces of a mosaic. Branching of the axons of single corticospinal neurons to supply multiple motoneuron pools has been directly visualized by labeling pyramidal axons with tracers and following the terminations to motoneuron pools in the spinal cord (Fig. 4).

Fig. 4. Transverse reconstruction of the terminal arborization of a hand area corticomotoneuronal axon in the C7 segment of the monkey spinal cord. This map was constructed from 12 serial transverse sections. The ulnar nerve motoneurons (upper two motor nuclei) and the radial nerve motoneurons (lower two motor nuclei) were labeled by retrograde transport of HRP. (From Shinoda et al. (1981)).

Another approach that has proven to be highly successful in demonstrating synaptic coupling between single corticospinal neurons and motoneurons is spike-triggered averaging of EMG activity (Fetz and Cheney, 1980; Porter and Lemon, 1993; Cheney, 2002). This method is particularly valuable because it can be applied in animals that are awake performing specific behavioral tasks. It is based on the rationale that if a neuron has a relatively direct synaptic linkage to motoneurons, the EPSPs or IPSPs associated with discharges of the cell will transiently raise or lower the firing probability of target motoneurons. These changes in firing probability can be detected by compiling averages of rectified EMG activity using spikes of the cortical cell as reference events. Because of the obligatory nature of transmission across the neuromuscular junction, muscle action potentials recorded as motor unit discharges directly reflect the spike train activity of motoneurons supplying the muscle. The transient increases in muscle activity observed in spike-triggered averages of EMG activity following the spikes of corticospinal neurons and other types of output neurons are referred to as PSpF and transient decreases as PSpS.

Using spike-triggered averaging of EMG activity, McKiernan et al. (1998) showed that 71% of cortical neurons involved in a reach-to-grasp task in macaque monkeys produced postspike effects (PSpF or PSpS) in multiple muscles. EMG activity was recorded from 24 muscles of the forelimb during task performance. It is also noteworthy that 45% of neurons tested facilitated some combination of muscles at distal (wrist and digit) and proximal (elbow and shoulder) joints. These synergies contribute to the patterns of distal and proximal muscle coactivation underlying performance of the reach-to-grasp task.

7. *The magnitude of corticospinal effects on motoneurons is strongest for distal muscles (wrist and digit) and weaker for proximal muscles (elbow and shoulder). Flexor and extensor muscles at the same forelimb joint show a similar pattern of influence (sign, strength and distribution) from corticospinal neurons.*

Early studies based on stimulation of the cortical surface in anesthetized primates were the first to demonstrate that EPSPs were smaller and more infrequent in motoneurons of proximal muscles than distal muscles (Preston and Whitlock, 1961; Langren et al., 1962a,b; Phillips and Porter, 1977; Porter and

Lemon, 1993). More recent intracellular recording work has confirmed these findings (Lemon et al., 2002). Studies of the magnitude of facilitation in spike and stimulus-triggered averages of EMG activity (see next section for description of methods) recorded from 24 forelimb muscles have led to similar conclusions and have provided more detail about input to specific muscle groups (McKiernan et al., 1998; Park et al., 2004). For example, the magnitude of poststimulus facilitation (PStF) in distal muscles (shoulder and elbow) was about 2.5 times that in proximal muscles (Park et al., 2004). Although some data from spike-triggered averaging shows a tendency for more common and slightly stronger facilitation of extensor muscles and suppression of flexor muscles from corticospinal neurons, the differences are relatively modest. In contrast, rubrospinal output is highly biased toward facilitation of extensor muscles and suppression of flexor muscles (Cheney et al., 1991; Mewes and Cheney, 1991; Belhaj-Saif et al., 1998).

8. *Corticospinal neurons show a clustered arrangement in the cortex rather than a uniform distribution. Clusters of corticospinal neurons in layer V may form the basis of functional cortical processing units that shape input–output organization in motor cortex.*

Corticospinal neurons have been labeled and visualized by injecting retrograde tracers such as HRP in the spinal cord. In such an experiment, Murray and Coulter (1981) reported that the labeled corticospinal neurons in SI and MI cortex were not distributed uniformly but rather show aggregations or clusters where cell density was higher than other locations (Fig. 5). The significance of such clusters is unknown but one possibility might be that clusters represent basic cortical input–output processing units in motor and somatosensory cortex.

This raises questions about what properties, if any, in addition to spatial location unite a group of cells as a functional unit. On the output side, the common property might be that cells of the same cluster share the same (or similar) muscle field, that is, the set of muscles facilitated or suppressed by the cell's activity. Evidence for this comes from spike-triggered averaging of EMG activity and an analogous method – stimulus-triggered averaging of EMG activity (Cheney and Fetz, 1985).

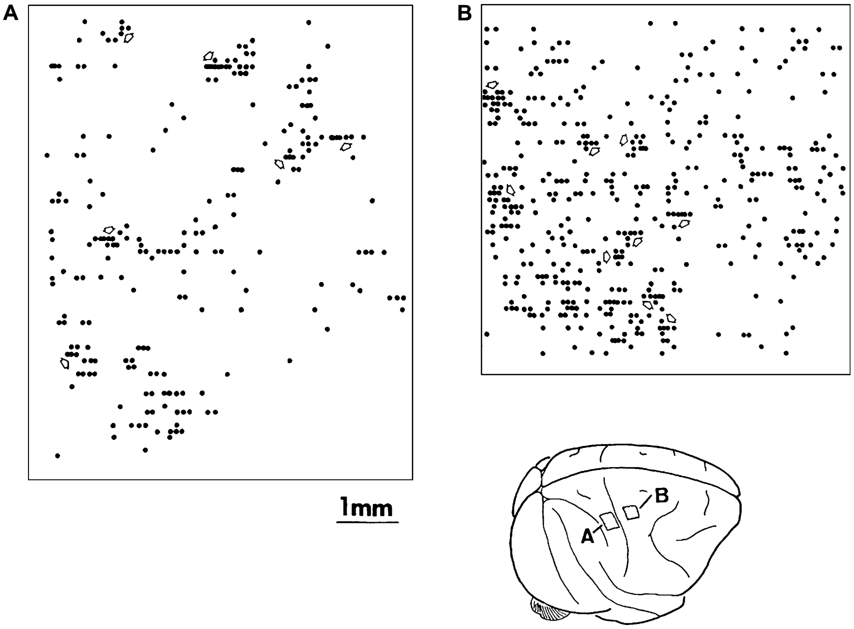

Fig. 5. Plots showing the clustering of labeled corticospinal neurons in the S1 cortex (A) and M1 cortex (B) following spinal cord injections of HRP in two macaque monkeys. Arrows indicate small clusters of cells that are often parts of larger aggregations. This clustering may form the anatomical basis for the functional clustering proposed by Cheney and Fetz (1985) in which corticospinal cells within a cluster have common target muscles (see Fig. 7). (From Murray and Coulter (1981)).

Stimulus-triggered averaging uses many of the same parameters as spike-triggered averaging except that the computer is triggered from microstimuli delivered at a low rate during movements (Cheney, 2002). Using a low rate of stimulation (5–20 Hz) avoids spread of excitation by temporal summation. Stimulation must be applied during active movements so EMG activity is present and coupled with averaging because the individual stimuli are generally subthreshold for discharging motoneurons. This method reliably detects both excitatory and inhibitory linkages. It is important to emphasize that the results obtained with stimulation reflect the summation of all the stimulated elements, including cell bodies activated directly by the stimulus, axon collaterals and afferent terminals on corticospinal neurons.

The combined application of spike- and stimulus-triggered averaging has provided significant new insight concerning fundamental features of the motor cortex output map. One of the most significant findings is that the pattern of poststimulus effects across different muscles usually closely matches the pattern of PSpF. Fig. 6 is an example in which PSpF was strongest not only in ED4,5 and EDC but was also clear in ECU based on an average of 14,000 spike events. A stimulus-triggered average computed from 500 microstimuli at 5 μA applied to the same cortical site showed PStF in the same muscles. Moreover, the rank order of PStF according to magnitude matched the rank order of PSpF. Although appearing comparable, the absolute magnitude of PStF was actually much greater than PSpF because it was obtained with only 500 stimuli compared to 14,000 spikes for PSpF. Because the signal-to-noise ratio increases as the square root of the number of trigger events, the PStF is actually about 5 times greater than PSpF. Whereas PSpF reflects the output organization of a single cell, PStF reflects the output effects of the population of cells and other neuronal elements that are excited by the stimulus. The fact that PStF involved many CM cells but has the same basic profile across synergist muscles as PSpF from the single CM cell at the same site suggests that neighboring cells activated by the stimulus have similar patterns of synaptic connections with motoneurons. The similarity in target muscle fields of neighboring CM cells has been confirmed by computing spike-triggered averages from adjacent cells simultaneously recorded through the same microelectrode (Cheney and Fetz, 1985).

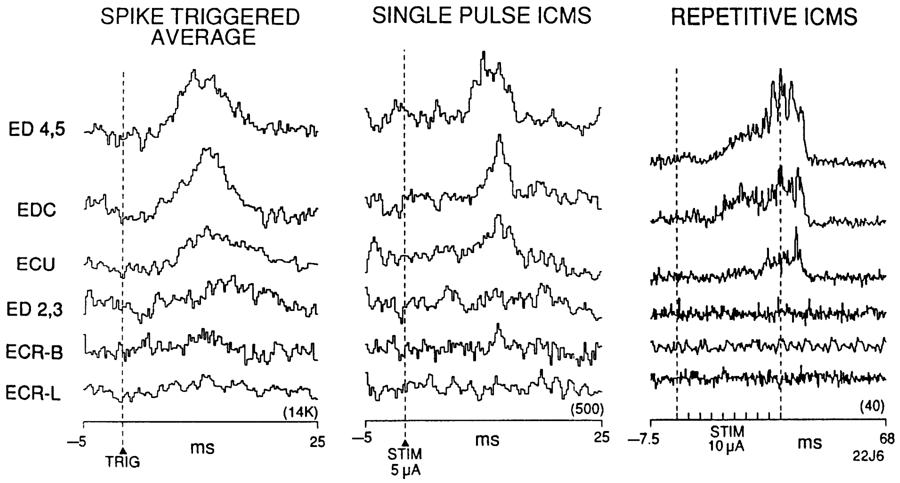

Fig. 6. Comparison of results obtained at a CM cell site with spike-triggered averaging of EMG activity, stimulus-triggered averaging of rectified EMG activity (single pulse ICMS coupled with averaging) and repetitive ICMS coupled with averaging. Repetitive ICMS consisted of 10 pulses at 330 Hz and 10 μA). Responses were averaged over 40 repetitions of the ICMS stimulus train. Effects in stimulus-triggered averaging were based on 500 trigger events and those in spike-triggered averages were based on 14,000 trigger events. Spike-triggered averaging revealed strong PSpFs in ED 4,5 and EDC as well as a clear but weaker response in ECU. No clear effects were present in the other forearm extensor muscles. Post-stimulus facilitation in stimulus-triggered averages matched the pattern of PSpF. In this case, the pattern of facilitation obtained with repetitive ICMS also matched the pattern of PSpF. (From Cheney (2002)).

Exceptions to the rule of similar output patterns with spike- and stimulus-triggered averaging do exist and may be more common for muscles of the hand (Lemon et al., 1987). Nevertheless, it seems reasonable to conclude that, just as neighboring sensory neurons in various parts of primary somatosensory cortex share common receptive fields, neighboring CM cells in lamina V of motor cortex often share common muscle fields. Moreover, these neighboring cells in lamina V of primary motor cortex may correspond to the clusters of cells observed anatomically by Murray and Coulter (1981).

Fig. 7 illustrates basic features of corticospinal output postulated by Cheney and Fetz (1985) for motor cortex. The basic module of output is a cluster of CM cells in layer V. Based on labeling studies, clusters may consist of 5–20 corticospinal neurons. The feature shared in common by each cell of a cluster is its muscle field. The similarity in synaptic output from different CM cells of a cluster seems to extend beyond the cell's simple muscle field. The fact that the relative magnitude of PSpF across different target muscles is similar for different cells in a cluster not only suggests a similar set of target muscles, but also suggests that the relative strength of synaptic input to target motor nuclei is also similar. The muscle fields of different clusters specify different muscle synergies; some facilitate a single motor nucleus (A), but most facilitate different combinations of synergist motor nuclei (for example, B and F). The most common output patterns for CM cells are pure facilitation, in which the cell has no effect on antagonist muscles (clusters A and C), and the reciprocal, in which the cells of a cluster not only facilitate agonist muscles but also simultaneously suppress antagonists, probably through

Fig. 7. Basic features of the motor cortex output map derived from studies with spike- and stimulus-triggered averaging. CM cells occur as clusters or aggregates in which each cell of the aggregate has the same or similar muscles field. (From Cheney and Fetz (1985)).

spinal inhibitory interneurons (B and E). Cells that cofacilitate both flexors and extensors are very rare in M1 but more common in red nucleus.

4.4. Cortical motor maps

9. The map of major body parts (areal representation) within M1 cortex shows consistent and orderly features as does the intra-areal representation.

The now famous homunculus drawn by Penfield and Rassmussen (1950) to summarize the results of their cortical stimulation experiments in humans has become one of the most recognizable illustrations in all of neuroscience. The homunculus is a generalization that represents the orderly somatotopic representation of major body parts in the precentral gyrus or motor strip. This is referred to as the areal representation (Porter and Lemon, 1993). The size of each body part is drawn to indicate the amount of cortical tissue devoted to movements of that part. While questions have been raised in recent years about the extent to which a consistent somatotopic organization exists in motor cortex, it is important to note that the existence of this basic areal somatotopic representation has not been challenged (Schieber and Hibbard, 1993; Sanes and Schieber, 2001; Schieber, 2001). Consistent features of this representation include the orderly sequence from medial to lateral along the precentral gyrus of representations for the foot in the mesial wall followed by the leg, trunk, arm, hand, face and tongue most laterally. Body parts involved in the most skilled movements have the most cortical tissue devoted to their control. These features of areal somatotopic organization were also clear from the classic mapping data of Woolsey (1958) in the monkey from which was drawn the well-known simunculus figures summarizing the representation of motor output.

What are the limits of somatotopic representation in motor cortex? The homunculus of Penfield implies the existence of an orderly representation of the digits in M1 with contiguous but separate zones devoted to them. The simunculus representation of Woolsey also implies a digit representation in M1 paralleling that found for somatosensory input from the hand to area 3b postcentral cortex (Cheney, 2002; Nelson et al., 1980). However, these summary figures are clearly extrapolations that go beyond the actual data that were collected. So to what extent might there be an orderly representation of parts within the forelimb or hindlimb? This is referred to as intra-areal somatotopic organization. For example, is there any orderliness in the representation of muscles or movements at different joints within the forelimb? This issue has been the topic of much discussion in recent years.

Regardless of the method used, mapping studies of primary motor cortex organization have almost universally emphasized the overlap of cortical sites producing activation of different individual muscles as well as sites producing movements at individual joints or movements of individual digits. These studies have suggested that there is no consistent intra-areal somatotopic organization whether the output measure is muscle activation or joint movements. This conclusion is supported by the elegant work of Schieber and Hibbard (1993) showing that the cortical area occupied by M1 neurons related to movements of different individual digits is almost completely overlapping.

However, while there is no consistent or orderly intra-areal map based on digit movements, maps of muscles belonging to different forelimb joints do, in fact, show consistent features of organization. This conclusion was reached by Park et al. (2002) based on stimulus-triggered averaging of EMG activity from 24 muscles of the forelimb in macaque monkeys performing a reach and prehension task. Cortical maps for individual muscles were analyzed to test for intra-areal consistencies in motor representation. Maps from four monkeys (Cheney et al., 2000; Park et al., 2004) revealed a consistent pattern in the representation of distal (wrist, digit and intrinsic hand) and proximal muscles (shoulder and elbow). Fig. 8 shows maps for two of these monkeys in which the cortical surface was unfolded and represented two-dimensionally. Note the core distal representation (blue) located largely in the bank of the precentral gyrus and extending to the border of cortical area 3a (S1 cortex). The distal representation is surrounded by a horseshoe-shaped representation of proximal muscles (red). He et al. (1993) reported a similar pattern of forelimb distal and proximal representation based on tracer injections in the spinal cord (see Fig. 2). A similar organization of distal and proximal muscle representations is also evident in data from the squirrel monkey (Strick and Preston, 1982; Nudo and Milliken, 1996; Nudo et al., 1992, 1996a,b). In the macaque monkey, based on repetitive ICMS, Kwan et al. (1978) described a concentric

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Fig. 8. (A) and (B) Cortical recording chambers implanted over M1 cortex in two monkeys. The coordinate system (5 mm grid) is overlaid in yellow and locations of electrode tracks are indicated with black outlined red dots. The large black rectangle overlying each chamber identifies the cortical area represented in maps C and D. In one monkey (lower chamber), a 15 mm incision was made in the dura for visual identification of the central sulcus. (C) and (D) Maps of motor cortex for each monkey represented in two-dimensional coordinates after unfolding the precentral gyrus. Maps were based on strong and moderate PStF effects together with R-ICMS evoked movements. Including weak PStF effects had little effect on map boundaries. (From Park et al. (2001)).

organization consisting of a central core of digit representation surrounded by concentric circular zones of increasing diameter for the wrist, elbow and shoulder. Maps from Park et al. (2001) differ from this description in that the proximal muscle representation is not continuous at the 3a/4 border and does not form a continuous circular zone. Moreover, Park et al. (2001) did not see clear separation of zones for digit and wrist muscles within the distal representation or separate zones for elbow and shoulder muscles within the proximal muscle representation. To conclude, consistent intra-areal features of forelimb motor output representation do exist and are evident most prominently in the separation of distal and proximal muscle maps.

Maps of individual muscles within the distal core representation show extensive overlap and in some cases noncontiguous "islands" of representation. Maps from He et al. (1993) based on tracer injections in the spinal cord suggest a substantial second representation of distal muscles in M1 cortex. However, no evidence for such a second representation could be found based on stimulus-triggered averaging of EMG activity from 24 forelimb muscles in the macaque monkey (Park et al., 2001).

A final point about Fig. 8 is particularly noteworthy. In addition to the core distal muscle representation (blue) and surrounding proximal muscle representation (red), Park et al. (2001) found a large zone separating these two representations where sites produced facilitation of both distal and proximal muscles (purple). The dimensions of this zone are not compatible with simple current spread from the pure distal and pure proximal representations. The existence of a specific zone with sites representing proximal and distal muscles in different combinations is consistent with results from spike-triggered averaging studies showing that about half of corticospinal cells involved in reach-to-grasp facilitate at least one proximal and one distal muscle as a synergy (McKiernan et al., 1998). What might be the function of such a zone representing both distal and proximal muscles in a variety of combinations? This question remains to be answered. However, an intriguing hypothesis is that this zone contains substrates for producing the muscle synergies underlying basic categories of coordinated, multijoint movements, for example, basic or primitive synergies for extending the limb and withdrawing the limb.

10. *Maps are not static but dynamic and are molded by use and injury.*

Maps of the representation of motor output from M1 tend to suggest a high degree of stability. However, it is important to recognize that these maps are dynamic and subject to both rapid and long-term forms of adaptive plasticity under a variety of circumstances (Donoghue, 1995; Seitz and Freund, 1997; Hallet, 1999). Adaptive plasticity and altered representation of movements and muscles in M1 has been demonstrated in relation to: (1) use and practice (Karni et al., 1995; Nudo et al., 1996a; Classen et al., 1998; Rioult-Pedotti et al., 1998), (2) immobilization (Liepert et al., 1995), (3) stroke-induced and other types of injury to motor cortex (Seitz et al., 1995; Nudo and Milliken, 1996; Nudo et al., 1996b; Cicinelli et al., 1997; Rouiller et al., 1998a,b), (4) spinal cord injury (Streletz et al., 1995; Bruehlmeier et al., 1998; Green et al., 1998), (5) limb amputation (Sanes et al., 1990a,b; Cohen et al., 1991; Fuhr et al., 1992; Kew et al., 1994; Ojemann and Silbergeld, 1995; Schieber and Deuel, 1997; Wu and Kaas, 1999), (6) altered somatosensory input (Keller et al., 1996; Rossini et al., 1996, 1998; Ziemann et al., 1998a,b; Hamdy et al., 1999), (7) muscle denervation (Sanes et al., 1990a,b), (8) repetitive electrical stimulation of motor cortex (Nudo et al., 1990), (9) exercise (Zanette et al., 1995), (10) synchronized use of thumb and foot movements (Liepert et al., 1999), and (11) development of implicit knowledge of a motor sequence (Pascual-Leone et al., 1994).

Motor cortex map plasticity has been demonstrated in animals using ICMS and in humans using TMS and functional imaging (Hallet, 1999). In interpreting the results of ICMS experiments, it is important to remember that this technique is thought to activate corticospinal neurons predominantly indirectly through synaptic inputs rather than directly (Porter and Lemon, 1993). Therefore, changes in maps observed with this method may result from intracortical circuit reorganization or excitability changes rather than changes in corticospinal terminal organization at the spinal level. This interpretation is reinforced by the findings of Huntley (1997) showing that rapid changes in map boundaries related to peripheral nerve cuts in the rat correlated with the spatial extent of horizontally projecting intracortical axonal projections. For example, 2 h after cutting the facial nerve supplying the vibrissal muscles in the rat, the forelimb representation had expanded 1.2 mm into the vibrissal representation. Consistent with this functional expansion, it was found that horizontal neuronal projections from the adjacent forelimb region extended 1.2 mm into the vibrissal area and presumably mediated the forelimb expansion after the facial nerve supplying the vibrissal muscles was cut. Stimulation outside the area containing intracortical horizontal projections from the forelimb representation failed to produce responses of either the vibrissae or forelimb in animals in which the facial nerve was cut. Similar shifts in map boundaries can be induced by injection of the GABA antagonist, bicuculline, suggesting that the excitability of these pathways is controlled by intracortical inhibitory mechanisms (Jacobs and Donoghue, 1991).

Use-related plasticity in M1 cortex parallels similar observations on plasticity in maps of primary somatosensory cortex associated with use. Nudo et al. (1996a,b) showed that training squirrel monkeys to perform a motor skill task produced an expansion in the map territories of muscles used in the task when compared to a task that required activation of the same muscles but without a requirement for skilled use of the digits. Similarly, immobilization has been shown to reduce the representation of the anterior tibial muscle compared to the unaffected leg (Liepert et al., 1995). Plasticity in motor maps has been reported both in relation to withdrawal and stimulation of somatosensory input. In humans, pharyngeal stimulation produced an expansion of the representation of the pharynx in motor cortex and a decrease in the esophageal representation lasting 30 min or more. These changes occurred in the absence of parallel changes in the excitability of brainstem-mediated reflexes suggesting that the source of plasticity was cortical in origin.

Anesthesia of the skin overlying a muscle reduces the cortical output representation of that muscle as demonstrated with TMS (Rossi et al., 1998). Ischemic deafferentation of the arm has been shown to produce a moderate increase in the size of the motor-evoked potential in the biceps muscle. This change was enhanced by conditioning low-frequency ($0.1\ \mathrm{s}^{-1}$) transcranial magnetic stimulation of the cortex on the side exhibiting plasticity and reduced by stimulation of the opposite cortex (Ziemann et al., 1998a,b). ICMS in the rat at a rate of $1\ \mathrm{s}^{-1}$ for 1–3 h produced expansion of the representation of the cortical area stimulated (Nudo et al., 1990). Borders shifted by 210–670 microns and changes were progressive and reversible.

Motor cortical map changes associated with ischemic or traumatic injury of the cortex have been demonstrated both in humans and in animals (Hallet, 1999). Nudo and Milliken (1996) produced ischemic lesions of identified representations of the cortical motor output map in squirrel monkeys by coagulating small arterioles entering the surface of the cortex. Motor cortex was mapped with a track spacing of 250 μm both before and a few months after ischemic lesions of primary motor cortex (M1). Subtotal ischemic lesions of the hand/digit representation resulted in a marked but transient deficit in use of the hand contralateral to the lesion, loss of digit representation in regions adjacent to the lesion and expansion of proximal muscle representations into zones that previously belonged to the digits. This loss of digit representation could be prevented by use of a "rehabilitative" training program in which the monkey was required to use the affected hand in a skilled motor task (Nudo et al., 1996b).

Limb amputation and deafferentation also evoked plastic reorganization of motor cortex with expansion of adjacent representations into the territory of the amputated limb but without loss of the somatosensory representation. Ojemann and Silbergold (1995) reported a case of forelimb amputation below the shoulder in a patient 24 years prior to neurological surgery for removal of a tumor in which primary M1 and S1 cortex were mapped. They found that representations of the face and jaw had moved medially and the shoulder representation had moved laterally, partially filling in the former arm representation. However, a zone remained between the jaw and shoulder representations from which no movements could be elicited. Phantom sensations were evoked from stimulation of the upper limb region of S1 cortex. These findings are consistent with those of Kew et al. (1994), who studied cortical blood flow changes based on positron emission tomography (PET) in patients with upper limb amputation. Shoulder movements on the amputated side produced blood flow increases over a wider area and greater magnitude in contralateral cortex than on the intact side. Fuhr et al. (1992) showed that muscles on the amputated side tended to be activated with TMS from a larger cortical region than the same muscles on the intact side. Motor-evoked potentials on the amputated side from contralateral cortex were also greater in magnitude and of shorter latency than the intact side. These changes could not be explained by changes in the excitability of the alpha motoneuron pools on the amputated side.

In conclusion, cortical motor maps cannot be viewed as static representations of output relationships. Rather, the size and strength of the cortical motor representation is dynamic and subject to influence from a variety of factors. Intracortical mechanisms are probably responsible for most examples of map plasticity. The extent to which corticospinal terminations with motoneurons may show plasticity is unknown.

4.5. Functional properties of the corticospinal system

11. *The discharge of corticospinal neurons is predictable based on knowledge of their muscle fields.*

Related to Principle number 10 above concerning the muscle fields (target muscles) of single corticospinal neurons is the question of how tightly coupled activation of a particular neuron is to coactivation of the facilitated muscles in its muscle field or reciprocal activation of the suppressed muscles. While this remains an area of active investigation, there is ample evidence that a cell's target muscle field is an important determinant of its activity under different task conditions. For example, cells with a reciprocal output pattern may not be activated for tasks such as power grip that require coactivation of flexor and extensor muscles at a particular joint (Fetz and Cheney, 1987). Cross-correlating the modulations in cortical cell activity with modulations in target and non-target muscle EMG activity showed that 90% of muscles with significant corticospinal PSpF have corresponding significant peaks in the cross-correlations of their activity (McKiernan et al., 1998). Similarly, 39% of target muscles with significant PSpS showed troughs when their activity was cross-correlated with that of the corticospinal cells producing the PSpS. The magnitude of PSpF was weakly correlated with the magnitude of the cell-muscle cross-correlation peaks. This analysis is based on correlations for individual corticospinal cell–target muscle pairs even though cells typically produce effects in combinations of multiple muscles.

It is known that forelimb cortical cells involved in reach-to-grasp can be divided into three broad types based on their muscle field distribution – those with muscle fields restricted to distal muscles, those with muscle fields restricted to proximal muscles and those with muscle fields that include a combination of distal and proximal muscles (McKiernan et al., 1998). Assuming that a neuron's muscle field is an important determinant of its movement-related modulation, one might predict that tasks producing largely distal muscle EMG activity would not engage the activity of neurons producing effects in only proximal muscles. Similarly, tasks involving activation of only proximal muscles would not engage the activity of neurons with distal only muscle fields. Finally, neurons with muscle fields consisting of combinations of distal and proximal muscles might not be activated for either the distal only or proximal only task because neither task is associated with coactivation of the neuron's complete muscle field. On the other hand, tasks such as reach-to-grasp that are associated with broad coactivation of both distal and proximal muscles might activate not only the neurons with combined distal and proximal muscle fields but also neurons with distal only and proximal only muscle fields. Belhaj-Saif et al. (2001) attempted to test this hypothesis by recording the activity of cortical cells with identified muscles fields under three tasks conditions that produced preferential activation of only distal muscles (isolated wrist movement task), only proximal muscles (forelimb push–pull task) or coactivation of both distal and proximal muscles (reach-to-grasp task). The results showed that neurons with muscle fields consisting of both distal and proximal muscles were much more heavily modulated for the reach-to-grasp task than for either task that involved modulation predominantly of only distal muscles or only proximal muscles. Neurons with only proximal muscle fields were not well modulated for the wrist task and neurons with only distal muscle fields were not well modulated for the push–pull task, although both these cell types were modulated for reach-to-grasp. These results suggest that a neuron's muscle field is an important determinant of its activity. In selecting neurons to participate in the execution of a movement, the central motor program must be "aware" at some level of the muscle fields of cortical cells or of functional clusters of cortical cells.

12. *Movements are produced by populations of corticospinal neurons acting in parallel with output from other descending systems. However, a relatively small number of motor cortex neurons is capable of reproducing 2D and 3D movement trajectories.*

Humphrey et al. (1970) first showed that correlations between cortical cell discharge rate and force or rate of change of force can be improved by considering a population of cells rather than any individual cell. Clearly, all movements involve thousands of cortical cells and, although the precision with which any given cell specifies a parameter of movement may show substantial variance, the sum total of the entire population of neurons involved in the movement specifies key parameters with little variance. Georgopoulos et al. (1982–1984) exploited this concept in a set of now classic studies using a 2D "center-out" task. In this task, the monkey begins by placing its hand on a central target. Movements are then cued to each of eight peripheral targets arranged equidistant around the central target while recordings are made of individual neurons in M1. The firing rate modulation of many M1 neurons was tuned to a particular direction of movement according to a cosine function. The contribution of each neuron to movement in a particular direction was plotted as a vector whose length was the change in firing rate for that movement direction, and whose direction was the neuron's preferred direction. Different cells were preferentially tuned to different directions of movement so all movement directions were represented. The contribution of each cell to movement in a particular direction was given by the cell's movement vector and these vectors could be summed to yield a population vector for that direction of movement. Of particular significance, it was found that the neuronal population vector for the activity of motor cortex cells is in the same direction as the actual movement. The original study of Georgopoulos was based on a population of 244 motor cortex cells. This work suggests that the direction of movement of the forelimb can be predicted on the basis of a relatively small number of neurons. These findings have important implications not only for the field of motor control but also for implementation of neural prosthetics.

This approach has also been extended to the analysis of movements in 3D space (Georgopoulos et al., 1986, 1988; Schwartz et al., 1988; Schwartz, 1994). These studies showed that the preferred directions of 224 neurons recorded in relation to proximal arm movements evenly represented all directions of 3D space. There was little or no tendency for preferential representation of any particular movement direction. These findings demonstrate that the directional tuning properties of motor cortex neurons generalize to 3D space and further demonstrate that neuronal population vectors can be robust predictors of actual movement direction.

This work is also significant in suggesting the feasibility of using activity from populations of motor cortex neurons in neuroprosthetic applications, for example, to control a robotic arm or a paralyzed arm. In a recent modeling study, Lukasin et al. (1996) showed that an artificial neural network could be trained to use experimentally recorded spike train data from a population of motor cortex cells to control a planar, two-joint, six-muscle simulated robotic arm. The actuator generated forces in close quantitative agreement with those exerted by trained monkeys. Moreover, output of the robotic arm could be controlled using as few as 15 motor cortical cells. Lin et al. (1997) tested a self-organizing feature model of the neural representation of arm trajectories based on neuronal discharge rates. The self-organizing feature model selects the optimal weights determining each neuron's contribution to an overall movement representation and can extract not only direction-related information but also other information carried in the discharge of neurons that may be relevant to movement control. Unlike the population vector method, this method has the advantage that it does not assume any linear relationships between discharge rate and parameters such as movement speed and trajectory curvature. Other studies of the number of neurons needed to accurately specify a movement trajectory suggest that considerable accuracy can be achieved with as few as 25 neurons depending on the task and the type of neurons used Georgopoulos et al. (1999).

Most recently, the feasibility of using the activity of a population of simultaneously recorded motor cortex neurons as well as neurons from other brain motor regions to control robotic arms has been tested in rats and monkeys (Chapin et al., 1999; Helms Tillery et al., 2003; Nicolelis, 2003; Taylor et al., 2003a,b). Schwartz et al. have recently trained monkeys to use activity from populations of motor cortex neurons to control movement of a robotic arm in 3D space. The accuracy with which goal-directed purposeful movements of the robotic arm could be achieved even with relatively small numbers of neurons was remarkable (Wolpaw et al., 2003).

13. *The discharge of corticospinal output neurons (corticomotoneuronal cells) is tightly coupled to aspects of movement execution and can best be viewed as specifying muscle-related parameters of movements such as EMG activity and force.*

A continuing controversy in motor control is whether movement direction is actually the parameter specified or encoded by motor cortex cells or if there is another more fundamental parameter (Georgopoulos, 1995; Loeb et al., 1996). This is also an issue for neurons belonging to other descending systems, although these systems have been less well studied than cortical neurons. Evarts (1968) originally showed that pyramidal tract neurons in motor cortex discharge at higher frequencies as the load opposing movement is increased. This finding has since been replicated in several other studies (Hepp-Reymond et al., 1978; Kalaska et al., 1989). Fetz and Cheney (1980) showed that, over a broad range, the rate of discharge of wrist-related corticomotoneuronal cells, identified on the basis of their PSpF of specific forelimb muscles, varies as a linear function of the torque produced. It has also been demonstrated that the activity of motor cortex cells, including the cosine tuning function, is heavily influenced by the load against which the monkey moves as well as arm posture (Cheney et al., 1988; Kalaska et al., 1989; Scott and Kalaska, 1995, 1997).

Nevertheless, many motor cortex cells show clear and reproducible directional tuning in center out tasks. However, cosine tuning curves of cell discharge can also be generated for responses made under isometric conditions so actual joint displacement and movement velocity are clearly not essential (Georgopoulos et al., 1992; Moran and Schwartz, 1999). Neuronal population tuning functions generated under isometric conditions could be interpreted as specifying the direction of isometric force. Moreover, individual muscles also show cosine tuning curves with best directions not unlike those reported for motor cortex cells (Georgopoulos et al., 1984) so clearly neurons with "muscle-like" activity would also exhibit this property.

This work has also served to emphasize the need to dissociate relationships to covarying parameters of force or other muscle-related variables and movement direction. When this has been done, primary relationships to muscle-related parameters such as force are evident for many neurons (Kakei et al., 1999) and this property may be characteristic of corticospinal output neurons (Cheney and Fetz, 1980). Primary relationships to movement direction have also been demonstrated for some neurons in M1, but it is not known if these were actual output neurons (Kakei et al., 1999).

Taken together, these findings support the notion that the most fundamental parameters encoded in the discharge of motor cortex cells, particularly cells with a demonstrable synaptic linkage to motoneurons, are parameters in a muscle-based coordinate system (Miller and Houk, 1995; Morrow and Miller, 2003). Additional support for this viewpoint comes from modeling studies, which demonstrate that directional tuning functions emerge as a natural and obligatory property of a system in which corticospinal output encodes relatively low-level parameters (muscle synergies and force) in a muscle-based coordinate system (Mussa-Invaldi, 1988; Todorov, 2000). Of course, this conclusion should not detract from the value of investigating directional tuning properties as a strategy for identifying the processing steps within different brain regions that transform sensory signals about the direction of movement needed to achieve a particular target to output signals that will yield the necessary timing and magnitude of muscle contraction at different joints to produce that movement direction. The neuronal population directional tuning approach also has great potential practical application in the implementation of neuroprosthetic devices (Cheney et al., 2000; Wolpaw et al., 2003).

14. Corticospinal neurons generally respond to sensory input from the body part that comprises the cell's motor field.

Three general principles have emerged from studies of input–output processing in motor cortex. First, stimulation within motor cortex generally produces movement of the body part containing the receptive field of neurons at the site of stimulation (Asanuma and Rosen, 1972; Rosen and Asanuma, 1972). Second, the cutaneous receptive field is generally located on the body surface in the direction of the movement produced by stimulation at that site (Rosen and Asanuma, 1972). In other words, the activity of a neuron will tend to produce movement in the direction of the neuron's receptive field. This may be a substrate for cutaneous feedback control of movements, particularly manipulative movements involving the hand. Consistent with this interpretation is the fact that lesions of primary somatosensory cortex are known to produce devastating impairments in voluntary movements of the contralateral hand, particularly exploratory movements guided by cutaneous input (Hikosaka et al., 1985). Finally, the third principle concerns the functional organization of proprioceptive sensory input to motor cortex neurons. Just as there is a spinal stretch reflex that opposes muscle lengthening, motor cortex neurons also respond in a similar way to muscle stretch and perturbations of movement. Corticomotoneuronal cells identified based on their PSpF of specific forelimb muscles are excited by stretch of the facilitated muscles (Cheney and Fetz, 1984). For example, cells that facilitate wrist extensor muscles are excited by perturbations that flex the wrist. The timing of these responses is consistent with a cortical contribution to the well-documented transcortical stretch reflex (Cheney and Fetz, 1984).

One final point regarding sensory input to M1 neurons deserves mention. There is a spatial separation of sensory input to M1 based on modality. Neurons in the rostral (anterior) half of M1 in primates tend to respond most strongly to "deep" proprioceptive inputs associated with passive joint movements and movement perturbations. These responses are probably dominated by muscle spindles, although Golgi Tendon Organ and other sensory afferents might also contribute. In contrast, sensory responses in the caudal part of M1 tend to be dominated by cutaneous inputs (Strick and Preston, 1978).

15. *Corticospinal neurons are essential for skilled distal movements and particularly independent use of the digits.*

The classic and elegant pyramidal tract lesion studies of Lawrence and Kuypers (1968a,b) demonstrated that the primary lasting deficit associated with pyramidal track lesions was a loss of the ability to move the fingers independently. Initially there was severe weakness, particularly distally, but this recovered to a significant extent. After several months of recovery, monkeys with pyramidal tract lesions were able to perform such tasks as climbing the walls of the cages with little difficulty. However, they were unable to use precision grip movements of the fingers to remove food pieces from circular wells cut in a board. Due to the invasiveness of the approach used by Lawrence and Kuypers to visualize and lesion the pyramidal tract, there have been few attempts to repeat these studies. Hepp-Reymond et al. (1974) showed that lesions of the pyramidal tract produce severe impairment of conditioned precision grip in the monkey. More recently, Chapman and Wiesendanger (1982) found that, with 66–87% destruction of the pyramidal tract unilaterally, monkeys showed recovery of arm and hand use to pre-lesion performance over a period of 4–5 weeks. Independent finger movements remained impaired and recovery of task performance was associated with the fact that the monkeys adopted a new strategy for removing food from wells in the Klüver board.

The few examples of relatively pure pyramidal tract lesions in humans have largely confirmed the lesion studies in monkeys although the extent of recovery of skilled movements of the hand and digits may be better than in the monkey (Bucy et al., 1964; Porter and Lemon, 1993). In one of the best-documented cases, Bucy et al. (1964) surgically lesioned the pyramidal tract unilaterally at the level of the cerebral peduncle in a patient suffering from hemibalismus. Immediately following the lesion there was cessation of voluntary movement. This was quickly replaced by a flaccid hemiplegia. There was continuous improvement in strength and coordination that plateaued after 7 months, at which time the patient was able to make "fine, individual movements of the digits" that were only slightly less well executed than on the unaffected side. It is astounding that interruption of a tract as large as the pyramidal tract would not produce more severe lasting deficits. This emphasizes the importance and role of extrapyramidal pathways involving descending systems other than the corticospinal system and the capacity for plastic reorganization. For example, Lawrence and Kuypers (1968a,b) noted that deficits associated with pyramidal tract lesions were less severe if the rubrospinal tract was intact. They suggested that the rubrospinal tract may compensate for loss of corticospinal neurons. This view was recently supported by Belhaj-Saif and Cheney (2000), who used stimulus-triggered averaging of EMG activity to show that the red nucleus output to forelimb muscles changes following pyramidal tract lesions in a manner consistent with the compensatory process hypothesized by Lawrence and Kuypers. In humans, a more significant ipsilateral corticospinal pathway than in monkeys may also play an important role in relatively rapid recovery of function.

16. *Corticospinal neurons are involved in a wide range of movements including those considered the most stereotyped and automatic.*

As discussed in the paragraphs above, it is clear that corticospinal neurons have their strongest actions on distal muscles and are very important for skilled use of the digits. Having established this, one might predict that cortical neurons might be little involved in the most stereotyped and automatic movements such as locomotion. However, large numbers of cortical neurons are heavily modulated during locomotion in the cat (Drew et al., 2002). Whereas these neurons are modulated for even the most stereotyped of locomotor tasks, it should be noted that the discharge becomes most intense when unpredictable obstacles are encountered and unplanned adjustments in the movement trajectory must be made.

Forelimb movements have been the focus of almost all the work that has been conducted in monkeys, so there are few studies relevant to this issue in primates. Although not the same as natural locomotion, two studies of cycling movements in primates have reported no difficulty in finding highly modulated neurons in primary motor cortex (Neafsey, 1980; Sahrmann et al., 1984).

4.6. Organization and functional properties of secondary cortical motor areas

17. *The SMA contains a complete motor map of major body parts, contains corticospinal neurons that terminate largely in the intermediate zone of the spinal cord, produces relatively weak direct output effects on muscle activity and has been implicated in a number of functions including movement sequence learning, movement programming and execution associated with postural control, coordination of bimanual movements and execution of internally guided movements.*

The SMA is located rostral to the precentral motor area, on the mesial wall of the hemisphere and on the dorsal bank of the cingulate sulcus (Fig. 9). The mesial wall is formed by two architectonic areas, SMA (F3) in the caudal portion and pre-SMA (F6) in the rostral portion (Matelli et al., 1991; Matsuzaka et al., 1992). SMA has traditionally been defined as the mesial agranular frontal cortex that corresponds to the medial part of Broadmann's area 6. Pre-SMA neurons are predominately related to sensory stimuli or the delay period between a stimulus and response, whereas neurons in SMA proper are more strongly related to aspects of movement execution. However, unlike the other premotor areas named above, pre-SMA lacks both a direct corticospinal projection and a projection to M1. Consequently, it does not meet the definition of a true premotor area. Evidence for these discrete corticospinal output zones is based in large part on exhaustive neuroanatomical labeling work (Dum and Strick, 1991, 1996; He et al., 1993, 1995; Galea and Darian-Smith, 1994), electrophysiological mapping studies (Preuss et al., 1996) and cytoarchitectonic studies (e.g. Matelli et al., 1991).

In addition to its corticospinal projection, SMA projects to the corresponding parts of the somatotopic representation of primary motor cortex, SMA and premotor areas bilaterally. It also projects to parietal cortex and basal ganglia. Input to SMA comes largely from the part of the thalamus (VLo) that transmits information from basal ganglia to cortex.

4.7. SMA terminations in the spinal cord

Dum and Strick (1996) made injections of WGA-HRP into SMA and showed that 77% of its terminations in cervical enlargement were on the contralateral side. Most of the terminations (87%) were confined to the intermediate zone (laminae V–VIII), 11% terminated in motoneuron pools of the ventral horn (laminae IX) and only 2% of the terminations were found in the dorsal horn (laminae I–IV). Twenty-three percent of SMA terminations were ipsilateral and these were located mainly in laminae VII and VIII.

Despite the fact that SMA has a large number of corticospinal neurons (40% that of M1), the termination pattern of SMA and M1 neurons in the hand and finger spinal motor nuclei is very different. The area occupied by M1 terminations in the hand spinal motor nuclei is about 13 times the size of that for SMA (Maier et al., 2002). EPSPs in motoneurons are also larger and more common from MI (88% of motoneurons) than from SMA (48% of motoneurons) (Maier et al., 2002). This is in agreement with the functional outputs of SMA studied with stimulus-triggered averaging of EMG activity showing that short latency facilitation and suppression from M1 is 12 to 28-fold stronger than that from SMA (Boudrias et al., 2003). Taken together, these findings suggest a very limited direct influence from SMA on motoneurons. The contribution of SMA corticospinal neurons to the control of movement might be achieved more through innervation of specific sets of spinal interneurons influencing separate functional spinal circuits rather than by direct or indirect actions on motoneurons.

4.8. SMA somatotopic organization

SMA is electrically excitable by relatively low-intensity currents (Table 1; Hummelsheim et al., 1986). Electrical stimulation studies of SMA show a somatotopic organization containing a complete body representation (Fig. 9). The face, forelimb, trunk, and hindlimb are arranged in a rostrocaudal manner with face rostral. (Mitz and Wise, 1987; Luppino et al.,

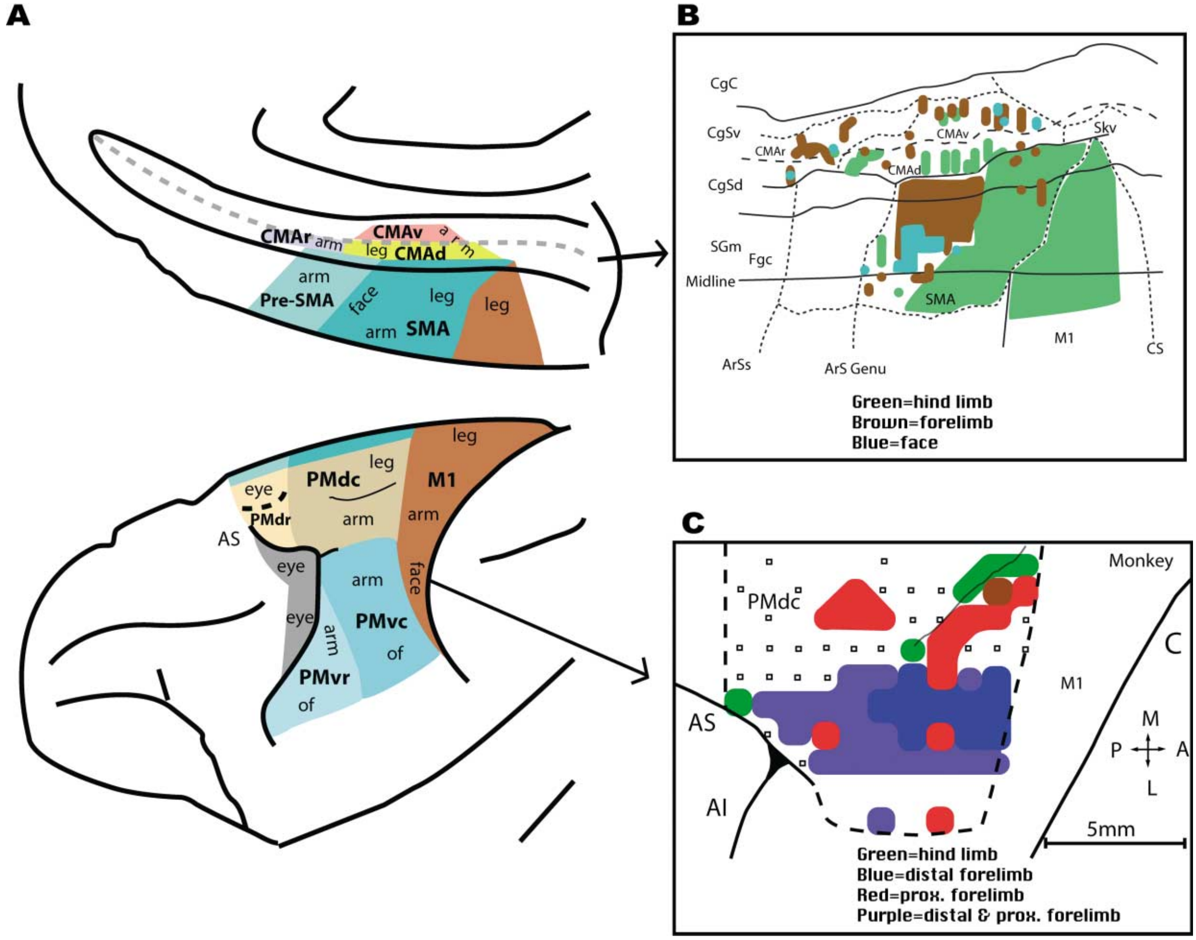

Fig. 9. Maps of motor output from frontal cortical areas based on ICMS evoked movements. (A) Somatotopic maps of frontal lobe motor areas including primary motor cortex (M1), SMA, CMAs and lateral premotor areas (PM). (B) Enlarged map of the somatotopic organization of SMA and CMAs on medial wall of the frontal lobe. The cingulate gyrus has been “unfolded” as a 2D map. (C) Enlarged map of the organization of PMdc showing the representation of the distal forelimb (blue), proximal forelimb (red), sites affecting both distal and proximal joints (purple) and hindlimb sites (green). Modified from Luppino et al. (1991), Luppino and Rizzolatti (2000) and Raos et al. (2003).

1991; Akazawa et al., 2000; Wang et al., 2001; Akkal et al., 2002).

While there is agreement about the somatotopic representation of major body parts, disparities exist in mapping data from ICMS-evoked movement studies. Luppino et al. (1991) reported a lack of segregation between proximal and distal movements with the majority of movements evoked from SMA involving proximal joints, typically in combination with other joints (complex movements). In contrast, others have emphasized that distal movements of the forelimb can be evoked from SMA with a frequency equal to the proximal movements and that isolated movements of single joints or single digits were as common as complex movements (Mitz and Wise, 1987). This conclusion agrees with the finding about equal numbers of presumed distal and proximal forelimb corticospinal neurons (Table 1).

4.9. Functions of SMA

A detailed review of functions of SMA is beyond the scope of this chapter. However, existing evidence strongly supports a role of SMA in various aspects of movement planning and execution including: (1) planning and executing movement sequences, (2) execution of internally guided movements, (3) coordination of bimanual movements, and (4) generation of anticipatory postural adjustments.

As discussed above, SMA has a large number of corticospinal neurons suggesting the potential for a direct role in movement execution. Clearly, SMA neurons become active during a wide range of simple movements (Fox et al., 1985), particularly internally guided (self initiated) movements, rather than externally cued movements (Passingham, 1987; Mushiake et al., 1991) and this further supports the notion that SMA could be a significant source, along with M1, of direct input to spinal motoneurons for the execution of at least some types of movements (Brinkman and Porter, 1979). However, recent evidence emphasizes the weak nature of the corticomotoneuronal component of SMA output and raises doubts about a role of SMA in execution of movement through its direct corticospinal projection (Maier et al., 2002; Boudrias et al., 2003)

SMA clearly seems to be involved in the generation of movement sequences. Early imaging studies showing activation of SMA during the performance of movement sequence tasks have provided some of the most compelling evidence for this function (Orgogozo and Larsen, 1979; Roland et al., 1980). The classic experiment of Roland et al. showed that SMA was activated bilaterally and M1 contralaterally when human subjects performed a memorized sequence of digit movements. Particularly interesting was the fact that when subjects were asked to mentally rehearse the sequence task without actually making any movements, SMA again was activated bilaterally suggesting a role in movement sequence planning rather than simple execution. Variations of this experiment have confirmed this result and have provided important additional details about the neural basis of movement sequence execution (Rao et al., 1993; Honda et al., 1998).

Substantial additional evidence for SMA's role in performance of movement sequences has come from reversible lesion and unit recordings studies in monkeys (Mushiake et al., 1990, 1991; Halsband et al., 1994; Jenkins et al., 1994; Tanji and Shima, 1994; Picard and Strick, 1996; Grafton et al., 1998; Shima and Tanji, 1998, 2000; Doyon et al., 2002) and 2-DG imaging studies in monkeys (Picard and Strick, 1997). For example, Tanji and Shima (1994) found a group of cells in SMA of monkeys whose activity was exclusively related to a sequence of movements performed in a particular order. They proposed that these cells contribute to a signal about the order of upcoming movements and are needed for planning and coding a sequence of movement several steps in advance. Neuronal activity in SMA gradually increases as experience with a particular movement sequence increases (Lee and Quessy, 2003).

In contrast to SMA proper, which appears to be involved in performance of learned movement sequences, pre-SMA may be involved in the actual learning of movement sequences (procedural memory). Hikosaka et al. (1996) used fMRI to image subjects learning a new sequence of button presses. During control scans, the subjects pressed the buttons in any order. They showed that a localized area in what was believed to be the human homologue of pre-SMA was particularly active for learning new sequential movements while SMA proper was active during performance of previously learned sequential movements.

Numerous unit recording, lesion and imaging studies have provided evidence that SMA is preferentially involved in self-initiated, internally guided movements versus externally cued movements. Mushiake et al. (1991) found that 65% of neurons in SMA were preferentially or exclusively involved in internally guided movements. In contrast, 64% of premotor neurons were more active during visually triggered movements. Moreover, Passingham (1987) reported that monkeys with bilateral lesions of SMA were unable to perform a simple arm-raising task to retrieve a food pellet but could perform the task if it was triggered by an auditory cue.

Evidence for a role in bimanual movements is also strong. Unilateral ablation of SMA in monkeys results in an initial clumsiness in use of the hands bilaterally but a long lasting deficit in bimanual coordination in which the two hands would assume the same posture rather than working cooperatively to accomplish the task (Brinkman, 1981, 1984). Interestingly, Brinkman found that the bimanual coordination deficit resolved with after cutting the corpus collosum and was only transient in animals with bilateral SMA lesions. This suggests that if SMA on one side is functioning, it may drive M1 bilaterally to produce the same movement and posture of the hands rather than the specific posture needed for successful performance of a particular bimanual task. A role of SMA in bimanual coordination has been confirmed in numerous more recent brain imaging studies in humans and single unit recording in monkeys (Kazennikov et al., 1999; Kermadi et al., 2000; Donchin et al., 2002; Nair et al., 2003).

Finally, there is evidence that SMA is involved in the control of body posture, specifically, generating proximal muscle responses necessary for the performance of distal limb movements (Travis, 1955; Denny-Brown, 1966; Wiesendanger, 1973, 1986; Tokuno and Tanji, 1993). This notion is supported by studies in human patients with damage to the dorsomedial aspects of SMA (Viallet et al., 1992). They show defective anticipatory postural adjustments associated with arm raising while maintaining an erect posture.

18. *Three separable motor areas (CMAs) are located within the cingulate gyrus beneath SMA. Two areas (CMAr and CMAv) contain motor maps of the forelimb, hindlimb and face, whereas CMAd appears to lack a representation of the face. CMA corticospinal neurons terminate largely in the intermediate zone of the spinal cord and have been implicated in a number of functions including reward-based motor planning and movement execution.*

The CMAs are located in the dorsal and ventral banks of the cingulate sulcus and consist of rostral (CMAr) and caudal (CMAc) divisions. CMAc is further subdivided into ventral (CMAv) and dorsal (CMAd) parts (Hutchins et al., 1988; Dum and Strick, 1991, 1996). The divisions of CMAs can be identified based on cytoarchitectural differences (Vogt et al., 1987; Matelli et al., 1991; Dum and Strick, 1996; Nimchinsky et al., 1996; Picard and Strick, 1996; Takada et al., 2001).

4.10. CMA terminations in the spinal cord

The pattern of CMAd and CMAv termination in the spinal cord is largely the same as SMA except for a lower overall density of termination. As with SMA, the majority of the terminations (90%) are located in the intermediate zone of the spinal cord (Dum and Strick, 1996). CMAd and CMAv show unique patterns of termination in the spinal cord suggesting distinct roles in the control of movement. CMAd terminations were most dense in the dorsolateral portions of the intermediate zone whereas terminations of CMAv were most dense in the dorsomedial regions. Projections to motoneuron pools exist but are relatively small (4%) and sparse terminations are present in the dorsal horn. Ipsilateral terminations are also observable in cervical segments (9–14%). To date, there are no data on the pattern of termination of CMAr corticospinal neurons in the spinal cord.

4.11. CMA somatotopic organization

The extent of topographic organization of each cingulate motor area is not entirely clear (Fig. 9). Only a few ICMS studies have explored both banks of the cingulate sulcus. A wide variety of face, forelimb, hindlimb, and trunk movements have been reported suggesting some degree of somatotopic organization. ICMS-evoked movements can be elicited most readily from CMAd, followed by CMAv and then CMAr (Mitz and Wise, 1987; Luppino et al., 1991; Akazawa et al., 2000; Takada et al., 2001; Wang et al., 2001; Hatanaka et al., 2003). The movements evoked in CMAd and CMAv tended to be restricted to a single joint or to the digits of one extremity. Those evoked from the forelimb were more proximal while those from the hindlimb were more distal. No distinct spatial segregation seemed to exist in the representation of distal and proximal movements (Luppino et al., 1991).

4.11.1. CMAr

The lower excitability of CMAr and its relatively small number of CS neurons (Table 1) compared to the other CMAs might explain the difficulty in establishing its precise somatotopy. The area from which forelimb movements could be evoked by ICMS is localized mainly in the ventral bank of the cingulate sulcus (Fig. 9). Fewer stimulation sites evoked trunk and hindlimb movements and these were mainly located caudally within the dorsal region of the cingulate sulcus (Luppino et al., 1991; Akazawa et al., 2000; Takada et al., 2001; Wang et al., 2001; Akkal et al., 2002; Hatanaka et al., 2003). A face representation has been reported in or near the rostral region of CMAr (Mitz and Wise, 1987). These aspects of somatotopic organization in CMAr are consistent with the results of a number of tracer injection studies showing that: (1) the rostral part of CMAr sends projections to the face representation of SMA and M1 as well as the facial nucleus in the pons (Muakkassa and Strick, 1979; Morecraft and Van Hoesen, 1992; Morecraft et al., 1996), and (2) the arm representation is mainly located in the ventral bank of the cingulate sulcus, caudal to the face representation. The proximal and distal forelimb representations were on both banks of the sulcus and overlapped ventrally. Only a few corticospinal neurons projected to the hindlimb.

4.11.2. CMAd

Tracer injections studies have shown that the representation of the forelimb in CMAd forms two separable regions (Fig. 9). Within the forelimb representation, the density of corticospinal neurons projecting to the distal segments was 4 times greater than those projecting to proximal segments. The hindlimb also has two separable representations interleaved between the forelimb representations, resulting in a rostrocaudal sequence of hindlimb–forelimb–hindlimb–forelimb (He et al., 1995).

This pattern is not clear in data from ICMS studies. Luppino et al. (1991) noted that the hindlimb representation was located mainly in CMAd and the forelimb representation in CMAv. In their studies, the hindlimb representation formed a long sagittal band that occupied a major part of the dorsal bank of the cingulate sulcus. In contrast, more recent studies have shown that the forelimb representation in CMAd is more prominent than that in CMAv and that the trunk and hindlimb representations are located in the rostral part of CMAd between the forelimb representations of CMAr and CMAd (Akazawa et al., 2000; Takada et al., 2001; Hatanaka et al., 2003). A cutaneous representation of the trunk (back) was also found in the rostral part of CMAd (Akazawa et al., 2000). Other than eye blinking evoked by two stimulation sites in the rostral part of CMAd of one monkey reported by Luppino et al. (1991), no other evidence of a facial representation in CMAd exists.

4.11.3. CMAv

Luppino et al. (1991) found that both hindlimb and forelimb movements could be evoked from CMAv, although the representation of the forelimb was substantially larger (Fig. 9). The forelimb representation was oriented in a manner paralleling the hindlimb representation in CMAd.

These findings are in agreement with tracer injection studies showing distinct corticospinal projections to a hindlimb and forelimb representation in CMAv with only 4% overlap (He et al., 1995). The forelimb representation was rostral to the hindlimb representation. Within the forelimb representation, distal segments were located caudally to the proximal ones with little overlap. Retrograde tracer injections in MI have identified an orofacial representation in CMAv (Tokuno et al., 1997).

4.12. Functions of cingulate motor areas

CMAr is thought to play a particular role in higher order aspects of motor behavior. This is supported by the fact that this area receives strong and direct input from the prefrontal cortex and the limbic system (Vogt and Pandya, 1987; Luppino et al., 1990; Morecraft and Van Hoesen, 1993, 1998). Evidence exists from a number of studies to support a role for CMAr in reward-based motor planning. For example, Tanji et al. (2002) identified four types of cells in the CMAr involved in responding to the quality of the reward, relaying that information to change planned movements, and preparing a new movement. This suggests a process occurring in CMAr that intervenes between detection of reward alteration and selection of a future movement.

Anterior cingulate cortex (ACC), corresponding to CMAr and CMAv in monkeys (Picard and Strick, 1996), is also thought to be involved in conflict monitoring. Brain imaging studies in humans show increased activation of ACC in the presence of conflict during information processing or response uncertainty, when errors are made and are more likely to be made (Carter et al., 1998; Botvinick et al., 2001; Braver et al., 2001; Van Veen et al., 2001; Gehring and Knight, 2002).

CMAd and CMAv seem to have a role in movement execution, particularly in the guidance of limb movement. Single unit activity recorded in CMAd and CMAv during an instructed delay task requiring combined shoulder and elbow movements showed that the two areas contain neurons with activity modulated in relation to visual cues (signal activity), the delay period (set activity) and the motor response (movement activity) in similar proportions and in all possible combinations within single cells. Neurons with only movement activity were more numerous in CMAd and CMAv compared to SMA and had a later onset and longer duration of movement activity suggesting a greater role in movement execution (Russo et al., 2002). Neurons in SMA were more likely to show both set and movement-related activity. Nevertheless, under the conditions of this forelimb task, the properties of neurons in CMAd, CMAv and SMA were most notable in their similarity.

19. *Two lateral premotor areas (PMd and PMv) are located in area 6 anterior to the hand/arm representation of M1. PMd contains a representation of the forelimb, hindlimb and face whereas only forelimb and face representations have been found in PMv. A substantial body of evidence supports a role for PMv in action understanding and imitation while PMd is involved in the selection and execution of voluntary actions based on sensory cues.*

The premotor cortex is located laterally in the frontal lobe and immediately rostral to M1 (Fig. 9). The boundary with M1 is defined by the absence of giant pyramidal neurons.

4.13. PMd and PMv terminations in the spinal cord

The terminal fields of PMd corticospinal axons have been examined electrophysiologically and anatomically in the monkey (Kuypers and Brinkman, 1970; Kuypers, 1982; Dum and Strick, 1991). The majority of PMd corticospinal axons terminate in the ventromedial intermediate zone of the spinal gray matter. The density of termination is less than that from M1 and SMA. Some fibers can be found within the motor nuclei of the ventral horn. The spinal terminations of PMv have not been systematically studied.

4.14. PMd and PMv somatotopic organization

Three studies to date have systematically mapped the lateral premotor areas using ICMS to evoke movements. Two of these were in the macaque monkey (Godschalk et al., 1995; Raos et al., 2003) and one was in the owl monkey (Preuss et al., 1996). The study by Raos et al. (2003) was limited to PMd. Considering PMv and PMd together, the general pattern of somatotopic organization appears to parallel that in M1 in both the macaque monkey and owl monkey (Fig. 9).

4.14.1. PMd

Stimulation studies of PMd (Godschalk et al., 1995; Raos et al., 2003) have focused mostly on its caudal part (PMdc or F2) and have revealed a hindlimb representation medial to the superior precentral dimple and a forelimb representation lateral to the dimple (Fig. 9). The threshold current required to evoke movement (Table 1) is higher in PMd than in M1 (Kurata and Tanji, 1986; Godschalk et al., 1995; Raos et al., 2003). Eye movements are represented in the rostral part of PMd (PMdr or F7) and in the rostral and lateral parts of PMdc (F2) (Preuss et al., 1996; Fogassi et al., 1999).

Godschalk et al. (1995) showed that the representations of proximal and distal muscles of the forelimb in PMd are largely overlapping. In a more recent study, Raos et al. (2003) showed segregation between proximal and distal movements with the proximal representation located more medially and distal movements more laterally. However, significant overlap was present, although less than that reported by Godschalk et al. (1995). The existence of a partially separable proximal and distal forelimb representation in PMd is in agreement with anatomical tracer studies (Dum and Strick, 1991; He et al., 1993).

4.14.2. PMv

Stimulation and anatomical tracer studies of PMv have also revealed a somatotopic organization, but one limited to the arm and the face (Fig. 9). No representation has been reported for the hindlimb (Dum and Strick, 1991; Godschalk et al., 1995). Thresholds for evoking movements with ICMS from macaque PMv are lower than for PMd (Gentilucci et al., 1988; Rizzolatti et al., 1988; Godschalk et al., 1995; Preuss et al., 1996). Rostral and caudal parts PMv can be distinguished based on the character of the movements evoked. The caudal part of PMv (PMvc or F4) shows a representation with the arm dorsally consisting mostly of proximal movements and a mouth representation ventrally (Kurata and Tanji, 1986; Gentilucci et al., 1988, 1989). Stimulation of PMvc (F4) often produces complex movements involving several adjacent joints. In the rostral part of PMv (PMvr or F5), stimulation and neuronal recording studies have also revealed separable hand and mouth representations (Kurata and Tanji, 1986; Gentilucci et al., 1988; Rizzolatti et al., 1988; Hepp-Reymond et al., 1994; Graziano et al., 1997). Hand movements are represented in the dorsal part of PMvr and the mouth is buried ventrally in the arcuate sulcus. However, there is a considerable overlap between the two representations (Gentilucci et al., 1988; Godschalk et al., 1995; Preuss et al., 1996).

4.15. Functions of lateral premotor areas

4.15.1. PMv

As mentioned above, recent evidence suggests that PMv should be subdivided into two areas – PMvr (F5) and PMvc (F4). PMvc is the selective target of the ventral intraparietal cortex (VIP) and PMvr is the selective target of the anterior intraparietal cortex (Rizzolatti and Luppino, 2001). PMvr (F5) has been extensively studied. The ventral premotor cortex (area F5) of the monkey contains a variety of neurons including ones that code goal-related motor acts such as hand and mouth grasping. Some of these cells are purely motor related while others respond to visual stimuli. A special and very interesting class of F5 neurons become active when the monkey makes a particular action (for example, grasping an object) and when it observes another individual (monkey or human) making a similar action (Fig. 10). These neurons typically respond neither to the sight of a hand making a similar action in the absence of the target nor to observation of the object alone, even if it has motivational interest for the monkey. These neurons represent a direct matching between the visual description of an action and its execution. In humans, the cortical area homologous to F5 is Broca's area. Despite being linked primarily to language, recent fMRI studies show that Broca's area is activated during hand movements (Iacoboni et al., 1999). Activation in three cortical areas – Broca's area, right anterior parietal region and right parietal operculum – was significantly stronger during imitation tasks (observing the task to be performed as a trigger to perform the same task, e.g. lift a finger in response to the same movement of the observed finger) than during observation/execution conditions in which the visual stimulus did not match the motor task to be performed. Rizzolatti et al. (2001) propose that F5 contains a "mirror system" in which internal motor copies of observed actions represent the neural basis for understanding the meaning of actions made by others, that is, how to use one's own peripheral motor apparatus to produce the same action as the one observed. Understanding an individual's intention in performing an observed motor act is different and is not what is represented in F5. Mirror neurons not only code motor acts but also allow imitation to take place. The mechanism of imitation includes retrieval of a motor act, construction of a sequence of motor acts and refinement of the motor sequence.

4.15.2. PMd

Like PMv, recent findings suggest that PMd can be subdivided into rostral (PMdr, F7) and caudal (PMdc, F2) subareas. Anatomical tracer studies show that

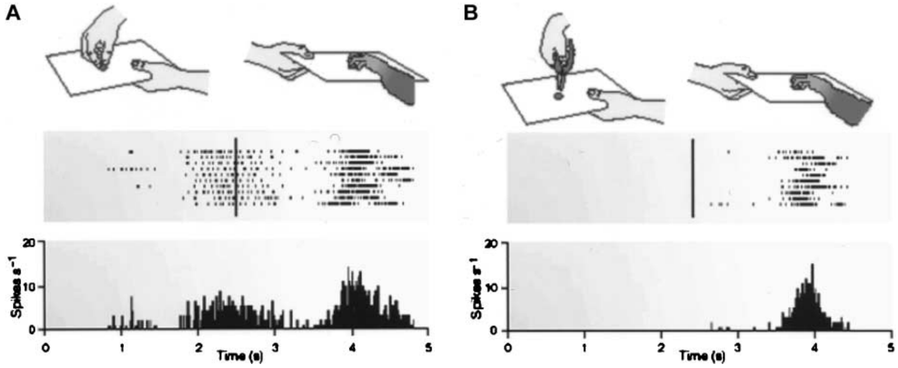

Fig. 10. Visual and motor responses of a mirror neuron in area F5. (A) A food morsel is placed on a tray and presented to the monkey. The experimenter grasps the food, then moves the tray with the food towards the monkey. Strong activation is present in F5 during observation of the experimenter's grasping movements, and while the same action is performed by the monkey. Note that the neural discharge is absent when the food is presented and moved towards the monkey without a grasping action by the experimenter. (B) A similar experimental condition except that the experimenter grasps the food with pliers. Note the absence of a neural response when the observed action is performed with a tool. Rasters and histograms show activity before and after the point at which the experimenter touched the food (vertical bar). (From Rizzolatti et al. (2001).)

PMdr receives a prefrontal input and does not send any appreciable projection to either M1 or the spinal cord. On the other hand, PMdc projects strongly to M1 and the spinal cord and receives only a small projection from the prefrontal cortex. The projections from prefrontal cortex to PMdc are limited to its rostral part (Matelli et al., 1998).

Lesion experiments, reversible inactivation and single unit recording studies in the primate have shown that PMd plays a major role in sensorimotor and cognitive processes necessary for the selection and execution of voluntary actions based on sensory cues (Passingham, 1985, 1988; Kurata, 1994; Wise et al., 1997). Lesions of PM cortex in monkeys result in difficulty using sensory cues to direct movement (Passingham, 1988). For example, in monkeys trained to pull a handle in response to a visual cue (blue light) or turn it in response to a different visual cue (red light), monkeys were still able to make the movement after removal of the PM cortex but were unable to select the correct movement in response to the visual cue. Adding a delay between the visual cue and the go signal further impaired performance in monkeys with PM lesions (Passingham, 1988). The lesions in these monkeys probably involved largely the PMd subdivision of premotor cortex.

These results are supported by findings from muscimol injections into PMd in which monkeys showed an increased number of directional errors in response to conditional sensory cues (Kurata and Hoffman, 1994) and other studies showing that PMd plays a crucial role in the visual guidance of movement, for example, the processing of sensory cues for movement selection (Kurata, 1994; Rizzolatti et al., 1998). Interpreting these results in relation to the subdivision of PMd, it appears that the ventro-rostral part (PMdr) uses somatosensory and visual information to control arm position during transport of the hand toward the target and the caudal part (PMdc) is involved in planning and controlling arm movements on the basis of somatosensory information alone (Rizzolatti et al., 1998).

Visual instructed delay tasks have been used extensively to study the functional properties of PMd neurons. Generally, in these tasks, first a visual stimulus is given to instruct the monkey about the required movement. This is followed by a variable delay period after which a go signal is given. Based on their activity during this task, PMd neurons can be grouped into three classes: (1) signal-related neurons active immediately after the instruction signal, (2) set-related neurons, which show sustained activity during the delay period and, (3) movement-related neurons that become active between the go signal and the onset of the movement. The distribution of these neurons in PMd is non-uniform. Johnson et al. (1996) showed that, in moving caudally from PMd to M1, the number of signal-related neurons decreased while the number of movement-related neurons increased. Set-related neurons represent more than 50% of the cells in PMd and are much more prevalent than in M1 (Kurata, 1989, 1994; Johnson et al., 1996; Wise et al., 1997). Set-related activity is sustained whether the instructional stimulus remains on or is turned off (see reviews of Kurata (1994) and Wise et al. (1997)). PMd set-related activity reflects aspects of preparation for a forthcoming motor action.

Cells in PMd discharge in relation to several parameters of reaching including direction and magnitude of movement (Wise et al., 1997). In a 3D limb movement task more than 90% of recorded neurons showed directional selectivity and the direction of the population vector corresponded very closely to the direction of the limb movement (Caminiti et al., 1991). PMd neurons are clearly more related to movement planning than to attentional or sensory processes (Wise et al., 1997; Rouiller et al., 1998a,b). Also, gaze angle modulates reach-related neuronal activity in PMd neurons (Rouiller et al., 1998a,b; Jouffrais and Boussaoud, 1999), although the overall effects on cell activity are generally modest because of the brief fixation periods associated with natural oculomotor behavior (Cisek and Kalaska, 2002).

In the ventral and rostral part of PMdc, recent observations have shown that neurons are driven by 3D visual stimuli (Fogassi et al., 1999). Information about the target location and the arm to be used can be integrated at a single neuron level to plan a forthcoming action (Hoshi and Tanji, 2002).

20. *Long-duration ICMS at many sites within M1 and premotor cortical areas elicits coordinated, purposeful movements. These movements can be represented as a single, continuous map of movement representation that encompasses both M1 and premotor areas.*

ICMS has developed as a method of examining motor output effects either in terms of movements evoked with short trains of high frequency, low intensity stimuli (e.g. 10 pulses at 330 Hz) or average

EMG responses associated with individual microstimuli (e.g. continuous 10–15 Hz pulses superimposed on movement performance). However, while this approach has advantages in terms of identifying effects related to the most direct output pathways, the duration of stimulation is much shorter than the duration of normal movements. Recently, Graziano et al. (Graziano et al., 2002a,b; Cooke and Graziano, 2003; Cooke et al., 2003) have applied high frequency ICMS to M1 and premotor areas for durations of 500 ms rather than the usual 30 ms, more closely matching the actual durations of natural movements. This has yielded some intriguing results that have provided a new concept of motor output organization in frontal cortex. This work has suggested the existence of a single unified map of the workspace around the body reaching across M1 and premotor areas (Fig. 11). The map can be viewed as containing three subregions from which different, seemingly purposeful movement responses can be elicited. These subregions have been mapped according to the final location of the hand resulting from long-duration stimulation. One subregion tends to bring the contralateral hand to locations in space in front of the chest. Stimulation within this part of the map evokes a variety of hand postures including a grip with the thumb against the forefinger, a fist, an open hand with all digits splayed, rotations of the wrist, and pronation or supination of the forearm, matching the natural behavior of monkeys during manipulation of objects within central space. This part of the cortex corresponds to the primary motor forelimb representation, an area that has long been known to emphasize the control of manual dexterity. A second subregion corresponds to hand locations at the mouth and stimulation within this region always produces a grip posture of the hand. These sites also generally cause the mouth to open. This area corresponds to area F5 (PMv) of Rizzolatti. A third subregion termed polysensory zone (PZ) contains neurons that respond to tactile stimuli on the face and arms, and visual stimuli near the face and arms. Stimulation of these sites evokes apparent defensive movements. This is a multimodal subregion that is largely within PMv. While these results are novel and intriguing, many questions remain concerning the mechanism of the responses and brain areas recruited, particularly with the long duration of stimulation and the relatively high ICMS currents.

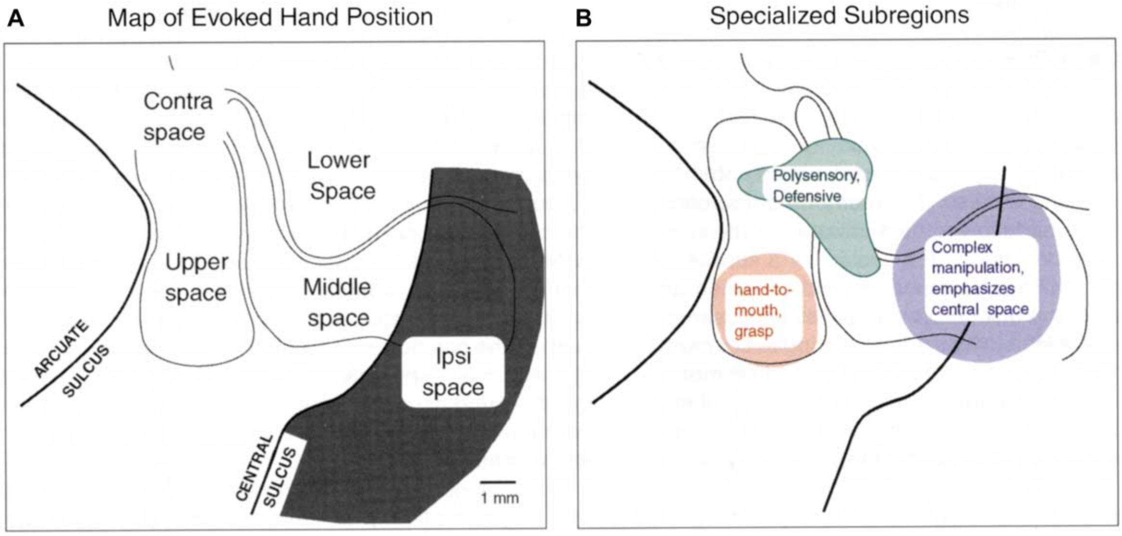

Fig. 11. Map of postures in the precentral gyrus obtained with high-frequency microstimulation on the time scale of a normal movement (0.5 s). (A) Stimulation at different cortical sites caused the hand to move to different positions in space around the body. The shaded region indicates buried cortex in the anterior bank of the central sulcus. (B) Subregions within the map of hand position that have specialized properties. The region labeled "polysensory defensive" (green) may correspond functionally to the dorsal part of area F4. The region labeled "hand-to-mouth grasp" (red) may correspond to part of area F5. The region labeled "complex manipulation emphasizes a central space" (blue) may correspond to the primary forelimb representation. (From Graziano et al. (2002).)

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