# The Organization of Behavioral Repertoire in Motor Cortex

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## Key Words

reaching, grasping, avoidance, locomotion, microstimulation

## Abstract

Motor cortex in the primate brain was once thought to contain a simple map of the body's muscles. Recent evidence suggests, however, that it operates at a radically more complex level, coordinating behaviorally useful actions. Specific subregions of motor cortex may emphasize different ethologically relevant categories of behavior, such as interactions between the hand and the mouth, reaching motions, or defensive maneuvers to protect the body surface from impending impact. Single neurons in motor cortex may contribute to these behaviors by means of their broad tuning to idiosyncratic, multijoint actions. The mapping from cortex to muscles is not fixed, as was once thought, but instead is fluid, changing continuously on the basis of feedback in a manner that could support the control of higher-order movement parameters. These findings suggest that the motor cortex participates directly in organizing and controlling the animal's behavioral repertoire.

## Contents

## INTRODUCTION

This review describes the cortical motor system from an ethological perspective. The monkey motor system is emphasized, although work on other animals is also considered. Certain actions may be typical of an animal's motor repertoire, such as reaching to grasp an object, manipulating an object with the fingers, putting an object in the mouth, or making defensive movements to block an impending object. How are these behavioral needs reflected in the motor circuitry? One potential risk in studying complex actions is that it might hinder a mechanistic or reductionist understanding of movement control. Traditionally, motor control is studied by examining simple components of movements. This review, however, argues that much greater insight can be gained about specific mechanisms when the motor system is considered in the context of meaningful behavior. The animal's behavioral repertoire is diverse, different behaviors require different control strategies, and at every level the motor networks are built and trained to produce those actions important to the animal. The topography of motor cortex, the specialized functions of cortical subregions, the properties of single neurons, and the connectivity between cortex, spinal cord, and muscles are all more approachable from an ethological perspective.

The review begins with a brief account of past and present views of motor cortex. The subsequent sections then outline the hypothesis that behavioral repertoire is systematically represented within motor cortex. Three levels of analysis are discussed:

1. Cortical topography: Motor cortex may be organized at least partly along ethological lines, in which subregions of cortex emphasize different categories of behaviorally useful actions.
2. Properties of single neurons: Individual neurons in motor cortex may be broadly tuned to idiosyncratic, complex patterns of motor output that reflect the animal's behavioral repertoire.
3. Mapping from cortex to muscles: The mapping from cortex to muscles is not fixed as was once thought, but instead is fluid, constantly changing on the basis

of feedback from muscles and joints. This feedback remapping may allow neurons in motor cortex to control almost any combination of high-level and low-level motor parameters needed to produce the diverse actions in the animal's repertoire.

## EVOLVING VIEWS OF MOTOR CORTEX

One hundred and thirty-five years ago, Fritsch & Hitzig (1870) borrowed Frau Fritsch's dressing table, lay an anesthetized dog on the tabletop, and electrically stimulated its cerebral cortex (Taylor & Gross 2003). They described an apparent map of muscles arranged in the frontal lobe. Shortly thereafter, Ferrier (1873) obtained a similar motor map in the monkey brain. By 1905, Campbell proposed that the primate cortex contained two motor areas, including a higher-order premotor area that controlled the lower-order muscle map. The cortical muscle map, in turn, controlled the spinal cord. This concept of a premotor area and a primary motor muscle map became the dominant view of the early twentieth century (e.g., Fulton 1938). (See **Figure 1*A***.)

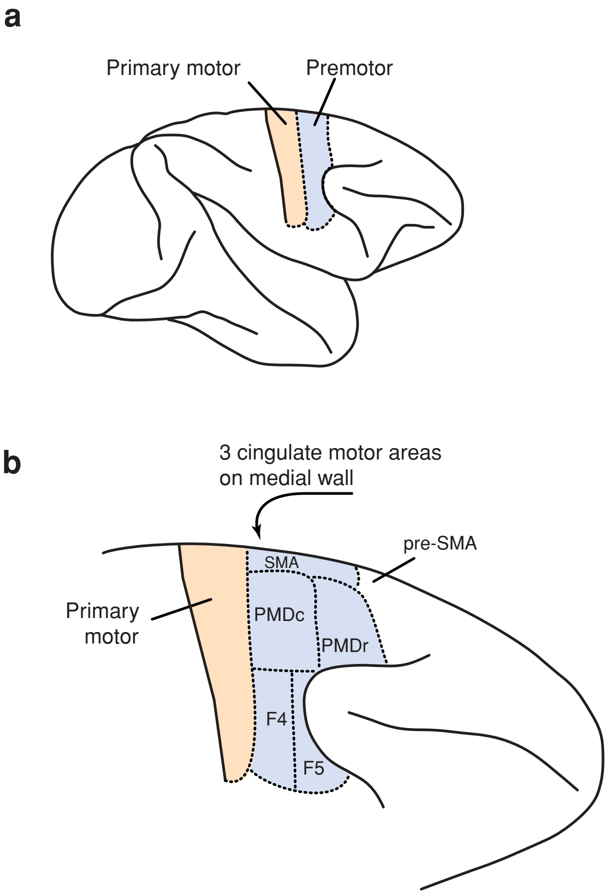

**Figure 1**

Early and recent views of the cortical motor system in the primate brain. *A*: One premotor area and one primary motor map of the body's muscles (e.g., Fulton 1938). *B*: A more modern view incorporating many premotor areas. A variety of terminology schemes are used including the F4 and F5 of Matelli et al. (1985), to designate the divisions of ventral premotor cortex, and the PMDc and PMDr of Preuss et al. (1996), to designate the divisions of the dorsal premotor cortex.

In some respects this early view has not changed. **Figure 1*B*** outlines a modern view, showing some of the cortical motor areas that investigators have described in the monkey brain (e.g., He et al. 1995, Luppino et al. 1991, Matelli et al. 1985, Matsuzaka et al. 1992, Preuss et al. 1996). In this scheme, the map in primary motor cortex controls movement at a simple level, perhaps controlling individual joints or small groups of muscles. This body map is influenced by many premotor areas that serve a range of higher-order functions. The premotor areas include ventral premotor cortex (sometimes divided into F4 and F5), dorsal premotor cortex (divided into a caudal and rostral division, PMDc and PMDr), the supplementary motor cortex (SMA), the pre-SMA, and three distinct motor areas in the cingulate sulcus on the medial wall of the hemisphere. The functions of these many premotor areas are debated. For example, Mushiake et al. (1990) suggested that SMA encodes sequences of movements. Wise (1985) suggested that PMDc participates in the planning and preparation of movement. Rozzolatti et al. (1988) suggested that F5 encodes a library of complex hand actions. Some premotor areas, including pre-SMA and PMDr, do not project directly to the primary motor cortex and thus may be less closely related to

**F4:** field 4 in motor cortex

**F5:** field 5 in motor cortex

**PMDc:** caudal division of dorsal premotor cortex

**PMDr:** rostral division of dorsal premotor cortex

**SMA:** supplementary motor cortex

**Pre-SMA:** region of cortex just anterior to supplementary motor cortex

motor output (Dum & Strick 2005, Lu et al. 1994, Tachibana et al. 2004).

The modern view includes a greater number of premotor areas than does the traditional view of the early twentieth century. Yet both views are similar in that they involve a cortical hierarchy in which premotor areas control various high-order aspects of movement, primary motor cortex decomposes movement into simple components in a body map, and these simple movement components are then communicated to the spinal cord for execution. Several lines of evidence suggest, however, that this basic hierarchical conception of the cortical motor system, which has persisted for more than a century, may require major modification. In particular, primary motor cortex may serve a more complex function than originally hypothesized, and some of the premotor areas may be on a similar hierarchical level as primary motor cortex.

First, the somatotopic map in primary motor cortex is overlapping, intermingled, and fractured, which suggests that it is organized to promote coordination among muscles and joints rather than to separate movements into constituent muscles and joints (Donoghue et al. 1992, Park et al. 2001, Sanes & Schieber 2001, Schieber 2002). Second, a high proportion of neurons in primary motor cortex are tuned to higher-order movement parameters and even sequences of movements, which suggests that it contains a more abstract code than a simple body map (Crowe et al. 2004; Georgopoulos et al. 1986, 1989; Kakei et al. 1999; Lu & Ashe 2005; Reina et al. 2001). Third, the distinction between primary motor cortex and some premotor areas has become blurred given that many of these areas project in parallel to the spinal cord (Bortoff & Strick 1993; Dum & Strick 1996, 2002, 2005; He et al. 1993; Wu et al. 2000). Fourth, the spinal cord itself controls movement at a level of complexity that far exceeds the map of muscles or joints proposed for primary motor cortex (for review of high-level spinal control of behavior see Bizzi et al. 2000 and Fetz et al. 2002). These findings have led to some uncertainty about the role of primary motor cortex and its relationship to premotor cortex.

An alternative way to understand the relationship among the cortical motor areas was recently suggested by a set of electrical stimulation experiments. We stimulated sites in the primary and premotor cortex of monkeys (Cooke & Graziano 2004a; Graziano et al. 2002a, 2003, 2004, 2005). Rather than use brief, 10- or 20-ms trains of electrical pulses that evoke muscle twitches, we used half-second trains, matching the approximate time scale of a monkey's reaching and grasping. The movements that unfolded during these long stimulation trains did not resemble muscle twitches or segregated joint rotations. Instead they were complex, involved many joints in coordination, and often resembled meaningful actions such as putting the hand to the mouth and opening the mouth, making a defensive gesture as if to ward off an impending impact, or reaching outward and shaping the hand as if to grasp an object (**Figure 2**). These different categories of movement tended to be evoked from different regions of cortex (**Figure 3**). Furthermore, the primary motor cortex and the caudal sectors of premotor cortex appeared to be at a similar hierarchical level, coordinating different but equally complex movements. Movements could not be consistently evoked from rostral premotor cortex.

These results suggest a new framework in which (*a*) the primary motor cortex is elevated from a map of muscles or joints to a representation of complex actions and (*b*) some of the caudal premotor areas currently recognized in the monkey brain are on a similar hierarchical level as primary motor cortex but emphasize different categories of complex movement. In this view, a mosaic of areas lies at the output stage of the cortical motor system, projecting directly to the spinal cord, influencing each other through lateral connections and representing the movement repertoire of the animal at a relatively high level. Other areas, such as the rostral premotor areas or parietal

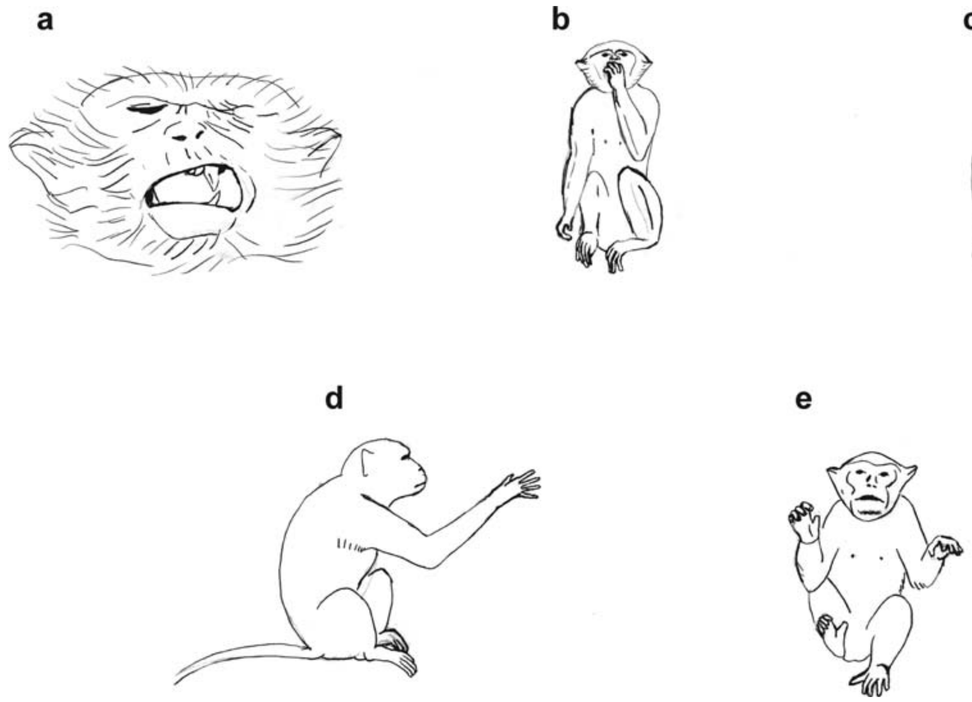

**Figure 2**

Five categories of movements evoked by electrical stimulation in motor cortex. Figure is drawn from video frames. Drawings represent the final posture obtained at the end of the stimulation-evoked movement. *A*: defensive-like posture of face. *B*: hand to mouth. *C*: manipulation-like shaping of fingers (precision grip) and movement of hand to central space. *D*: outward reach with hand opened as if shaping to grasp. *E*: climbing- or leaping-like posture involving all four limbs.

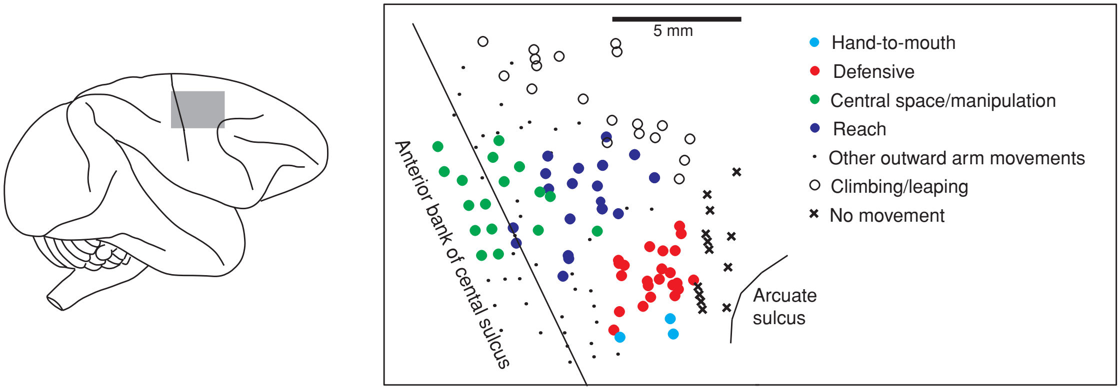

**Figure 3**

Topographic arrangement of stimulation effects in an example monkey. Rectangle on schematic brain shows approximate location of studied cortex, spanning the arm and hand representation in the medial-lateral extent and spanning the precentral gyrus in the anterior-posterior extent. Diagonal line in map indicates lip of central sulcus, and the area left of the line indicates unfolded cortex in the anterior bank of sulcus. Curved line indicates approximate location of arcuate sulcus. Sites are color-coded according to type of complex movement evoked. Adapted from figure 10 of Graziano et al. (2005).

motor areas, may serve other even higher-order functions.

## ELECTRICAL STIMULATION ON A BEHAVIORAL TIMESCALE

Much of the evidence discussed below involves cortical stimulation. This section therefore briefly outlines the history of stimulation on a behavioral time scale and its use in probing motor function.

### Widespread Use of Long Stimulation to Probe Function

Ferrier (1873) was the first to apply long stimulation trains to the motor cortex of monkeys and obtained complex "purposive" movements including a hand-to-mouth movement. Ferrier's observations, however, were not pursued, and most subsequent stimulation studies of motor cortex used brief stimulation to probe the somatotopic map (e.g., Foerster 1936, Fulton 1938, Penfield & Boldrey 1937, Woolsey 1952). Although Penfield reported spectacular and complex effects of cortical stimulation in humans, including some apparently meaningful movements evoked from the supplementary motor cortex, he continued to view the lateral motor cortex as a body map from which only muscle twitches could be evoked. In 1954 he wrote, "It would seem that the awkward gross movements produced by stimulation of the hand, tongue, and leg areas of the precentral gyrus give no more than an indication of the peripheral connexions of those portions of the gyrus. There is no suggestion that the acquired skills which are at the disposal of man have any form of true representation there."

These early studies used surface stimulation, a spatially crude technique. By the 1960s, surface stimulation was largely replaced by more focal stimulation through microelectrodes. This improved technique of microstimulation was used to study a diversity of brain systems. Stimulation trains up to 3 min in duration were used to evoke eating, drinking, sex, and aggression from specific regions of the hypothalamus (e.g., Caggiula & Hoebel 1966, Hoebel 1969). In these experiments, the duration of the train was critical for allowing the full behavior to unfold because when the stimulation ended, the evoked behavior stopped. Stimulation trains on the time scale of a normal saccade (30–80 ms) were used to probe maps of evoked eye movements in cortical and subcortical oculomotor structures (e.g., Bruce et al. 1985, Robinson 1972, Robinson & Fuchs 1969, Schiller & Stryker 1972, Tehovnik & Lee 1993, Thier & Andersen 1998). Stimulation in these oculomotor areas on a time scale shorter than a normal saccade, such as for 20 or 10 ms, resulted in a truncated saccade (Stanford et al. 1996). Stimulation for up to 500 ms evoked coordinated head and eye movements in the superior colliculus and the SMA (Chen & Walton 2005, Freedman et al. 1996, Martinez-Trujillo et al. 2003). Stimulation in the arcuate sulcus for 1000 ms evoked smooth pursuit eye movements (Gottlieb et al. 1993). Stimulation of visual and somatosensory cortex for 1000 ms was used to alter perceptual judgments of sensory stimuli (e.g., Romo et al. 1998, Salzman et al. 1990). In each of these studies, stimulation helped establish the behavioral role of the tested brain area. In most cases, stimulation provided the initial insight into the function of the studied area, thereby pointing the way for the use of other techniques such as single neuron recording.

In motor cortex, stimulation on a behavioral time scale was not widely used until recently. Asanuma and colleagues used microstimulation to study the motor cortex of cats and monkeys (e.g., Asanuma 1975, Asanuma et al. 1976), but these experiments were limited to brief stimulation trains, typically less than 20 ms. The purpose of the experiments was to evoke muscle twitches and study the somatotopic map in motor cortex. Microstimulation on a behavioral time scale was not used until Huang et al. (1989) obtained rhythmic, chewing movements in monkeys by applying 3-s stimulation trains in the mouth representation. The method was then relatively neglected in the motor system until our stimulation studies in monkeys suggested a possible mapping of complex movements in the precentral gyrus (Cooke & Graziano 2004a; Graziano et al. 2002a, 2003, 2004, 2005). We found that short stimulation trains evoked muscle twitches as previously reported; however, when the stimulation train was extended to 500 ms, the muscle twitches unfolded into complex, multijoint movements that appeared to have a behavioral meaning. We chose to stimulate for 500 ms because neurons in motor cortex typically have elevated activity throughout a movement, and a 500-ms time scale matches the duration of a monkey's normal reaching and grasping.

Stimulation on a behavioral time scale has now been used to evoke complex, apparently meaningful movements from a variety of species. In the parietal lobe of prosimians, stimulation for 500 ms evoked a range of complex movements including hand-to-mouth movements, defensive-like movements, reaching movements, and aggressive displays (Stepniewska et al. 2005). These different categories of movement were clustered in separate cortical regions in a manner similar to the clustering we obtained in the motor cortex in monkeys.

In the rat motor cortex, stimulation of even a single neuron was able to evoke oscillatory movements of the whiskers (Brecht et al. 2004). In one subregion of the whisker representation, stimulation for 500 ms evoked rhythmic, exploratory-like whisking movements, whereas stimulation of an adjacent cortical subregion evoked a retraction of the whiskers and a possible defensive-like closure of the eye, contraction of the facial musculature, and lifting of the forepaw (Haiss & Schwarz 2005). These findings suggest rat motor cortex may be similar to monkey motor cortex in being organized partly around ethologically relevant functions.

Stimulation of cat motor cortex for 500 ms evoked reaching movements of the forepaw (Ethier et al. 2004), which suggests that cat motor cortex may also be partly organized around ethologically relevant movements.

## Spread of Signal Through Connected Networks

Injecting a train of current pulses into the brain is artificial. This artificiality by itself is not a fatal flaw. Most experimental techniques involve artificial manipulation. The lesion technique, for example, is particularly invasive. Can useful insight be gained from the stimulation technique, despite (or perhaps because of) the artificiality of the manipulation? Its track record, discussed above, suggests that wherever it is used in the brain it results in critical insight into function.

The standard microstimulation technique involves a train of low amplitude pulses delivered through the electrode tip. The pulses are brief (e.g., 0.2 ms) and are presented at a high frequency (typically ranging from 50–500 Hz). The amplitude varies depending on the brain area or behavior under study but is typically below 500 microA. Most studies use biphasic pulses (a negative followed by a positive phase) to balance the charge and thus eliminate electrolytic damage to the neural tissue. Stimulation is thought to activate physiologically relevant brain circuits. In this view, the directly stimulated neurons around the electrode tip do not have any specific function by themselves; rather, their function is a consequence of their connections with and influence on a wider network.

Using microstimulation in the study of the motor cortex of cats and monkeys, Asanuma and colleagues attempted to isolate the most direct, descending pathway from cortex through the spinal cord to the muscles (e.g., Asanuma 1975, Asanuma et al. 1976). Unfortunately, each point in motor cortex has widespread connections. In addition to the direct descending pathway to the spinal cord, motor cortex neurons have lateral connections to neighboring cortical neurons, connections to other cortical areas, and connections to a variety of subcortical structures. Many of these targets of the motor cortex also project directly to the spinal cord. Thus stimulation of motor cortex does not only activate the descending pathway to the spinal cord, but also activates other, diverse pathways through the motor network. Asanuma and colleages used brief stimulation trains hoping to limit the spread of signal through lateral networks, but they could not eliminate the possibility. Jankowska et al. (1975) showed that brief stimulation trains, and even single stimulation pulses, evoked signal spread laterally through the cortex as well as downward to the spinal cord.

The problem of isolating the most direct descending pathway from cortex to the muscles was not solved until Cheney & Fetz (1985) measured the latency between the onset of cortical stimulation and the onset of muscle activity. They obtained latencies as short as 5 ms, presumably reflecting the most direct pathway.

These stimulation studies in motor cortex therefore focused on anatomical tract tracing and moreover focused on isolating the specific, most direct pathway from cortex to the spinal cord and to the muscles. For these reasons the experimenters were generally concerned with the "problem" of signal spread through lateral networks. However, the lateral connections through the motor network are not artifacts. They are presumably critical for normal function. When stimulation is used on a behavioral time scale, the signal is assumed to spread through the pre-existing connections, thereby partially mimicking the function of the directly stimulated tissue.

Does the stimulation signal actually spread through pre-existing circuits, or is it so unnatural that it spreads in a meaningless jumble? Tolias et al. (2005) addressed this question by stimulating primary visual cortex (V1) in monkeys and measuring the signal spread with functional magnetic resonance imaging. Because the connections of V1 are well-known, the spread of activity evoked by stimulation could be compared with the spread expected from pre-existing connections. The results suggested that stimulation, even of long duration (4000 ms) and high amplitude (1400 microA), activated surrounding and distant cortex in a specific pattern that closely matched the known pre-existing anatomical connectivity. Thus even though stimulation is artificial, driving the neurons near the electrode tip at high frequency in a sustained fashion, it results in a spread of signal through physiologically meaningful pathways. It is presumably this recruitment of physiological circuits that allows stimulation to roughly mimic the function of the directly stimulated tissue.

The strength of the stimulation technique is that it is causal. The evoked movement provides an immediate hypothesis about the function of the activated tissue. In this sense it is more powerful and direct than single neuron recording, which depends on interpreting correlations. One of the weaknesses of the stimulation technique is that it is not spatially precise. The electrode directly stimulates a ball of tissue that can be a millimeter or more in diameter. The technique provides a rough sense of function, perhaps averaged over the neurons near the electrode tip. It may help to orient researchers in the right direction for the use of other experimental techniques. The most convincing experimental approach is to combine techniques, such as stimulation, single neuron recording, and chemical activation and inactivation. In some regions of motor cortex this combining of techniques has been employed, greatly strengthening the case for the representation of complex, ethologically relevant movements.

## MOTOR CORTEX TOPOGRAPHY IS ORGANIZED PARTLY AROUND ETHOLOGICAL CATEGORIES

This section describes in detail the hypothesized parcellation of the macaque motor cortex into subregions that emphasize different categories of action. It also describes the possible incorporation of these subregions into an overarching topographic map.

## Defensive Movements

Stimulation within a restricted zone in the precentral gyrus (red dots in **Figure 3**) evoked a coordinated set of movements that resembled a defensive reaction to an impending impact or an unexpected touch (**Figure 2*A***). The movements were mainly contralateral to the stimulating cortex and included a blink, a squint, lifting of the upper lip in a facial grimace, folding of the ear against the side of the head, shrugging of the shoulder, turning aside of the head, a blocking movement of the arm, and a distinctive, defense-related centering movement of the eyes (Cook & Graziano 2004a, Graziano et al. 2002a). These movements matched the components of a normal defensive reaction such as when the monkey's face is puffed with air (Cooke & Graziano 2003).

To probe further the relationship between this cortical area and the control of defensive movements, we chemically manipulated the brain region and tested the animal's defensive reactions to an air puff (Cooke & Graziano 2004b). When the region of cortex was injected with muscimol, a gamma-aminobuteric acid (GABA) agonist that inhibits neuronal activity, the monkey exhibited a specific reduction in its defensive reactions. In contrast, injections of bicuculline, a GABA antagonist that disinhibits neuronal activity, caused an enhancement in the defensive reactions.

In further support of the interpretation that this cortical zone contributes to the defense of the body surface, neurons in this region of cortex typically respond to tactile stimuli on the face and arms and to visual stimuli looming toward the tactile receptive fields (Fogassi et al. 1996, Gentilucci et al. 1988, Graziano et al. 1997, Rizzolatti et al. 1981). Some of the neurons are trimodal, responding also to auditory stimuli in the space near their tactile receptive fields (Graziano et al. 1999). Because of these distinctive sensory properties, we refer to this cortical region as the polysensory zone (PZ). Although all monkeys tested have a PZ, it varies among animals in size and precise position (Graziano & Gandhi 2000). It is typically located just posterior to the bend in the arcuate sulcus. In the terminology scheme of Matelli et al. (1985), it probably corresponds to the dorsal part of premotor area F4, where similar polysensory neurons have been reported (Fogassi et al. 1996, Gentilucci et al. 1988, Matelli et al. 1985).

**PZ:** polysensory zone (in the precentral gyrus)

**VIP:** ventral intraparietal area

PZ probably receives its sensory input from the posterior parietal lobe and may receive a particularly dense projection from the ventral intraparietal area (VIP) (Lewis & VanEssen 2000, Luppino et al. 1999). Indeed, VIP and PZ have nearly identical properties. Just as in PZ, neurons in VIP have tactile receptive fields typically on the face or arms, and a high proportion of neurons also respond to visual and auditory stimuli in the space near the tactile receptive fields (e.g., Colby et al. 1993, Duhamel et al. 1998, Schlack et al. 2005). Electrical stimulation of VIP evokes defensive-like movements that resemble those evoked from PZ, although higher currents are required in VIP and the movements are less consistent (Cooke et al. 2003, Thier & Andersen 1998). We suggest that a major emphasis of this distinct parieto-frontal circuit is the construction of a margin of safety around the body and the selection and coordination of defensive behavior, although it may contribute to other behaviors as well (Graziano & Cooke 2005).

## Hand-to-Mouth Movements

In another cortical zone within motor cortex (light blue dots in **Figure 3**), stimulation evoked a characteristic hand-to-mouth movement (**Figure 2*B***). The grip aperture closed during stimulation, bringing the forefinger against the thumb; the forearm supinated and the wrist flexed such that the grip was aimed at the mouth; the hand moved precisely to the mouth; and the mouth opened. These four movement components occurred simultaneously in a smooth, coordinated fashion resembling the monkey's own voluntary hand-to-mouth movements. The hand speed followed a distinctive bell-shaped velocity profile in which the speed rose to a single peak near the middle of the movement and then decelerated smoothly to the end of the movement (Graziano et al. 2005). This bell-shaped velocity profile is typical of normal voluntary hand movements (Flash & Hogan 1985). When a weight was fixed to the hand, the stimulation-evoked movement apparently compensated for the added load and usually brought the hand to a similar final position as without the weight (Graziano et al. 2005). Thus the evoked movements had a certain complexity and sophistication of control. However, if an obstacle was placed between the hand and the mouth, the hand bumped against the obstacle and pressed against it without moving intelligently around the obstacle. Thus the evoked movements had limited flexibility. Once the hand reached the mouth, it remained at that location with no further movement until the end of the stimulation train. Similar movements could be evoked in awake or anesthetized animals, although the movements were weaker and required greater current in anesthetized animals.

In all monkeys tested, the hand-to-mouth sites were clustered in a zone lateral and sometimes anterior to PZ. In the terminology scheme of Matelli et al. (1985), these sites may lie within ventral area F4 or caudal area F5. Neurons in F5 respond during grasping with the hand and mouth and during interactions between the hand and mouth (Murata et al. 1997; Rizzolatti et al. 1988).

## Central Space/Manipulation

Stimulation of another cluster of sites (green dots in **Figure 3**) caused the hand to move into a restricted region of central space within ~10 cm of the chest and the fingers to shape in a specific manner (**Figure 2*C***). These finger movements included an apparent precision grip (thumb against forefinger), a power grip (fist), or a splaying of the fingers accompanied by a turning of the palm toward the face. The movements resembled the types of actions that monkeys typically make when manipulating or examining objects in central space (Graziano et al. 2003). These sites were clustered in a posterior zone that lay partly on the gyral surface and partly on the anterior bank of the central sulcus. This cluster probably corresponds to the traditional primary motor hand representation. It may also correspond to the core region in the motor cortex maps of Kwan et al. (1978). In these maps based on brief stimulation trains, Kwan et al. found a posterior region of cortex that emphasized the fingers and hand, surrounded by a belt region that emphasized more proximal musculature. This core hand region has since been confirmed by others (e.g., Park et al. 2001). In our studies, using longer stimulation trains, we found that stimulation of the core region not only caused movement of the fingers, but also often caused movement of the arm that brought the hand into a large region of central space. We suggest that this cortical zone may represent a "manual fovea," a repertoire of movements that is related to the manipulation of objects and heavily biased toward hand locations in a central region of space in front of the chest (Graziano et al. 2003).

## Reach

For some cortical sites (dark blue dots in **Figure 3**), stimulation evoked an apparent reach in which the wrist straightened, the fingers opened as if to grasp, and the hand extended outward to a region of space distant from the body (**Figure 2*D***). For these movements, again, the hand speed followed a distinctive, natural bell-shaped profile. Also when a weight was fixed to the hand, the stimulation-evoked movement apparently compensated for the added load, usually bringing the hand to a similar final position as achieved without the weight (Graziano et al. 2005). These apparent reaching sites tended to be located on the gyral surface just anterior to the central space/manipulation zone and dorsal to PZ. Because of this relative location, the reach-related sites probably lay within the dorsal premotor cortex, within its caudal division (PMDc), where a high proportion of neurons respond in relation to reaching movements (e.g., Crammond & Kalaska 1996, Hocherman & Wise 1991, Johnson et al. 1996, Messier & Kalaska 2000). Typically stimulation of more rostral sites did not evoke reliable or clear movements.

On the basis of connectional anatomy and using brief stimulation trains to probe somatotopic maps, Strick and colleagues (Dum & Strick 2002, 2005; He et al. 1993) described three hand-related zones in the lateral motor cortex: a primary motor hand area, a ventral premotor hand area, and a dorsal premotor hand area. Our results using longer stimulation trains match this proposed set of three hand areas. We find a central space/manipulation zone, a hand-to-mouth zone, and a reach zone, all three emphasizing movement of the fingers in addition to movement of the arm. We suggest that these hand-related areas differ from each other, at least partly, by emphasizing different behavioral functions.

## Climbing/Leaping

In a large medial and anterior region (open circles in **Figure 3**), stimulation evoked especially complex movements that involved the arm and leg. These movements were often bilateral. Because the monkey was anchored in a primate chair, these full-body movements were constrained and difficult to interpret. Subjectively, the movements resembled climbing or leaping postures. Whether this functional interpretation is correct, it is clear that this medial, anterior region is qualitatively different from the more lateral regions because it involves an integration of movements of both sides of the body and of the arms, hands, legs, and feet. It is not yet clear whether this region of cortex lies within the most dorsal part of dorsal premotor cortex, or within the SMA, or both. Neurons that respond bilaterally during reaching have been reported in dorsal premotor cortex (Cisek et al. 2003), and brief stimulation of SMA evokes complex multilimb movements (e.g., Luppino et al. 1991, Mitz & Wise 1987, Wu et al. 2000).

## Other Outward Arm Movements

In addition to the reaching movements described above, at many sites (small black dots in **Figure 3**) stimulation drove the hand to a distal location but without evoking any clear opening of the grip. In the sense that there was no obvious specific behavioral purpose, this type of stimulation-evoked movement was the most general and vague of the responses we obtained. These sites were not clustered in a single zone but instead were scattered, surrounding the reaching sites and the central space/manipulation sites.

## Stimulation-Evoked Movements Reflect Movement Repertoire, Not a Single Movement Parameter

Stimulation of motor cortex usually drives the arm to a specific final posture regardless of the starting posture. As a result, the hand usually moves toward a goal position in space (**Figure 4**). Here we suggest two possible explanations for this convergence of the arm to a posture. The second hypothesis is more likely than the first.

One hypothesis is that the stimulation-evoked postures reflect a fundamentally posture-based strategy for movement control. Such posture-based control strategies, in which movements are coordinated by first determining the desired final posture and then planning the trajectory to that posture, have been proposed by many other investigators (e.g., Desmurget & Prablanc 1997, Feldman 1986, Giszter et al. 1993, Rosenbaum et al. 1995). Initially, we also interpreted the stimulation results as evidence for a posture-based control strategy that might be generally used

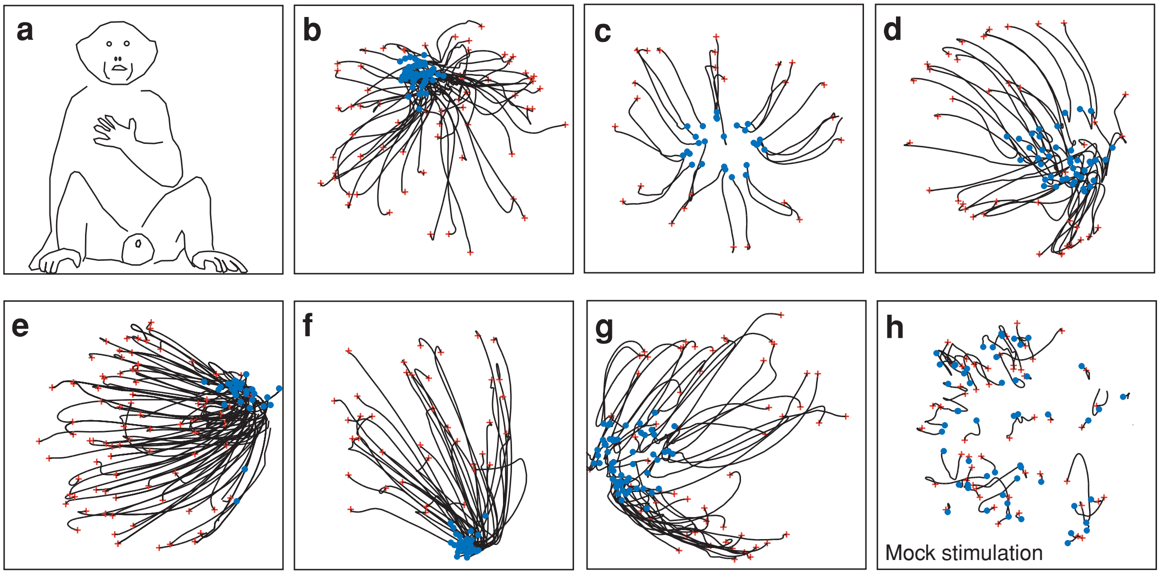

**Figure 4**

Examples of hand movements evoked by microstimulation in motor cortex. *A*: The monkey drawing indicates the approximate size and location of the monkey within the square frame. The height of the frame represents 50 cm. *B–G*. Stimulation-evoked hand movements from 6 typical stimulation sites. Movement measured in 3-D at 14.5-ms intervals by using tracking markers. Each thin black line shows the path of the hand during a stimulation train. The red + indicates the start of the movement. The blue dot indicates the end of the movement. In a small number of trials, the tracking markers were transiently blocked from the view of the camera because of the specific posture of the limb. In these cases, the trace is interrupted. For all stimulation sites, the hand tended to move from a range of initial positions toward a more restricted final region of space. *H*: result of mock stimulation in which the wires to the electrode were disconnected but all other aspects of the testing were the same. Adapted from figure 1 of Graziano et al. 2005.

for all movement (Graziano et al. 2002b). However, given the diversity of movements in the animal's repertoire, and the diversity of movements evoked by stimulation, it seems increasingly likely to us that the motor cortex does not use one fundamental control strategy but rather controls any parameter needed to guide behaviorally useful actions.

A second possible explanation is that stimulation tends to evoke movements common in the monkey's normal repertoire. In this interpretation, moving the arm to a posture in order to stabilize the hand is a common action for monkeys and therefore is often evoked by stimulation. Our observations of monkeys in the home cage and monkeys in group-housed zoo environments are consistent with this second hypothesis. We videotaped monkeys and analyzed the videos frame by frame (Graziano et al. 2003). The arm spent most of its time stabilizing the hand in a region of space while the hand performed an action. For example, the arm often stabilized the hand at the mouth while the fingers and wrist moved to act on a food item. During the manipulation of objects in central space, the arm stabilized the hand in front of the chest. During the grooming, the arm maintained a narrow range of postures while the hand and fingers acted on the fur of another monkey. The arm often supported the monkey's weight by maintaining a posture in which the hand was braced on the floor or a branch or a part of the cage. These results suggest that moving the arm to a posture and maintaining that posture within narrow limits while the hand performs

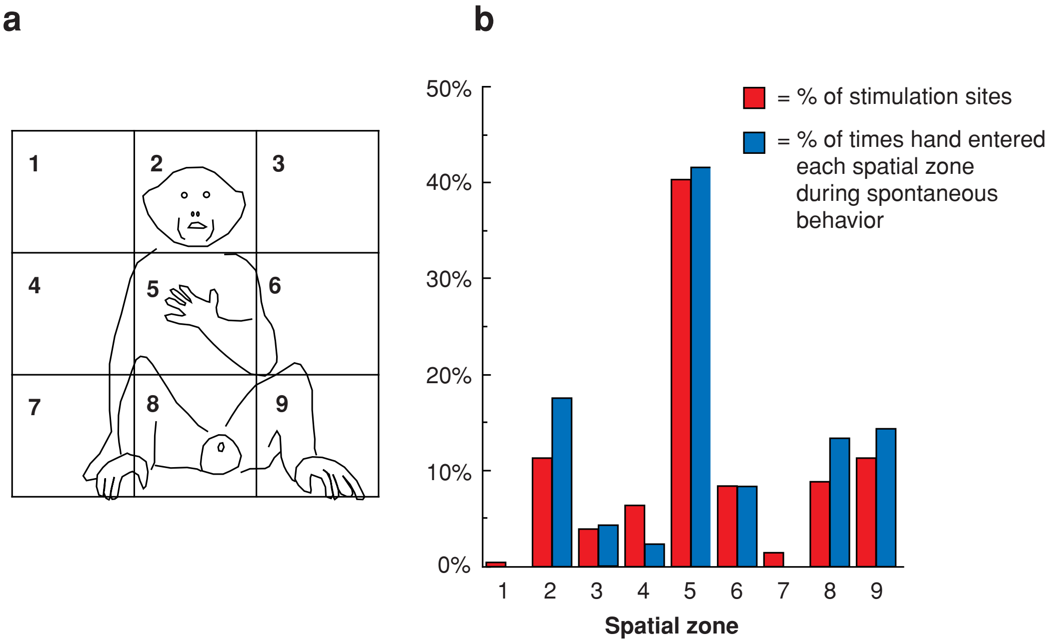

**Figure 5**

Distribution of hand location during spontaneous behavior in the home cage. *A*: On each video frame, the location of the hand was determined within an imaginary 3 × 3 grid around the monkey's body. This spatial assessment was made relative to the midpoint of the chest. Each square in the grid was 12 cm across. *B*: Blue bars show the proportion of times that the hand entered each spatial zone during spontaneous behavior. Red bars show the proportion of stimulation sites in the precentral gyrus for which stimulation drove the hand into each spatial zone. The two distributions are significantly correlated (regression analysis, $F = 119.13$, $P = 0.0004$).

an action is a common, behaviorally useful strategy.

To further probe whether the stimulation-evoked movements reflect the monkey's natural repertoire, we compared the distribution of hand positions evoked by stimulation with the distribution of hand positions observed during spontaneous behavior (Graziano et al. 2003). As shown in **Figure 5**, the space in front of the monkey was divided into nine imaginary zones. The red bars in the graph show the percentage of stimulation sites that caused the hand to move into each spatial zone. Zone 5, just in front of the chest, and zone 2, near the mouth, were particularly well represented. The blue bars show the results for the monkey's spontaneous behavior in the home cage. The spontaneous behavior closely matched the stimulation-evoked behavior. Those hand positions common in the monkey's spontaneous repertoire were also commonly evoked by stimulation of motor cortex. These results add further support to the hypothesis that the stimulation-evoked movements reflect the monkey's normal behavioral repertoire.

Recently researchers have proposed that the motor system uses an optimal control strategy (Scott 2004, Todorov & Jordon 2002). In this hypothesis, if a specific task requires fine control of a particular movement parameter, then the control strategy will target that parameter. For example, in hitting a nail with a hammer, the final position of the hammer head is of critical importance and is highly conserved across trials, whereas other variables such as the exact trajectory of the hand or the speed of rotation of the arm joints are less important and are more variable across trials. In the optimal control hypothesis, there is no single, preferred parameter for motor control, such as direction or end posture or joint speed. Instead, the parameters being controlled depend on the task being performed. Studies involving a directional reaching task may tend to reveal a directional control strategy (e.g., Vindras et al. 2005), whereas studies involving more posture-based tasks tend to reveal a more postural control strategy (e.g., Desmurget & Prablanc 1997, Rosenbaum et al. 1995). We suggest the reason why stimulation of motor cortex tends to evoke a final posture of the arm is because the animal often engages in tasks in which end posture is of particular importance.

Consider, for example, a hand-to-mouth movement evoked by stimulation. The movement of the arm to a goal posture might reflect the specific requirements of this behaviorally useful action. The stimulation also evokes an opening of the jaw and lips, a grip-like movement of the fingers, and a speed profile of the hand that approximately matches the speed of a natural hand-to-mouth movement. Stimulation therefore does not merely specify an arm posture; it specifies the set of parameters relevant to that particular action. As another example, in the rat motor cortex, stimulation of a specific region evokes rhythmic whisking movements that match the rat's natural movements (Haiss & Schwarz 2005); in this case, the behaviorally useful action does not involve movement to a posture but rather involves a fundamentally different set of movement parameters.

If motor cortex reflects the monkey's behavioral repertoire, then will training the animal on a different repertoire result in a different organization of motor cortex? This question remains to be explored. There is some evidence that the primary motor cortex in neonatal kittens contains a segregated somatotopy and that, during experience, the map develops the overlapping and intermingled topography characteristic of the adult (Martin et al. 2005). Thus the organization of motor cortex by ethological function may be at least partly entrained through experience, modifying a simpler, original somatotopic map.

## Overarching Maps Within Motor Cortex

The previous sections describe a possible parcellation of motor cortex into separate subregions, each one emphasizing a different category of movement. Do these subregions fit together into a larger topography?

Kohonen (1984) suggested that cortical maps may self-organize on the basis of the pattern of inputs and activity of local circuitry. The self-organization tends to optimize nearest neighbor relationships such that neurons that process similar information are located near each other in cortex and are therefore more interconnected and require shorter transmission delays. Self-organization can lead to fractured or apparently disordered maps in certain cases, owing to the fact that the cortex is two dimensional, yet the relevant parameter space may be of higher dimensionality. This concept of self-organizing maps was used to explain the complex organization of primary visual cortex (Durbin & Mitchison 1990) in which line orientation, ocular dominance, and retinotopy interact to produce a complicated and irregular pattern of cortical swirls (Obermayer & Blasdel 1993). Likewise, some of the apparent disorder in the map in primary auditory cortex has been attributed to a self-organization influenced by many competing parameters (Schreiner 1995). Motor cortex may also be influenced by several competing parameters resulting in a fractured, complex topography.

The large-scale organization of motor cortex is somatotopic. Most studies describe a rough body map with some overlap between the representations of different body parts, some fractures in the representations, and some rerepresentations (e.g., Donoghue et al. 1992, Ferrier 1873, Foerster 1936, Fritsch & Hitzig 1870, Fulton 1938, Gould et al.

1986, Kwan et al. 1978, Park et al. 2001, Penfield & Boldrey 1937, Strick & Preston 1978, Woolsey 1952).

Embedded within this larger somatotopy, within the arm and hand representation, lies a rough map of hand location that can be obtained with electrical stimulation (Graziano et al. 2002a,b). An example map for one monkey is shown in **Figure 6**. Lateral sites correspond to hand locations in upper space, such as hand-to-mouth sites; sites more medial along the central sulcus correspond to hand locations in mid-level space; and the most medial sites correspond to hand locations in lower space, sometimes resembling a bracing of the hand on the floor to support the body's weight and sometimes resembling a reach into lower space. There is also some topographic order in an anterior-posterior dimension, in which more anterior sites correspond to more distal and lateral hand positions and more posterior sites correspond to hand positions closer to the midline of the body. Stimulation deeper in the central sulcus sometimes drives the hand across the midline to the opposite side of space. This rough map of hand location seems to unify the primary motor cortex and the caudal parts of premotor cortex into one supermap. However, though we find the map of hand location in every monkey, it is variable and noisy within as well as between animals. Different hand locations overlap considerably in cortex, as attested by the size of the error bars in **Figure 6**. Like the somatotopic map, the hand-location map is statistical.

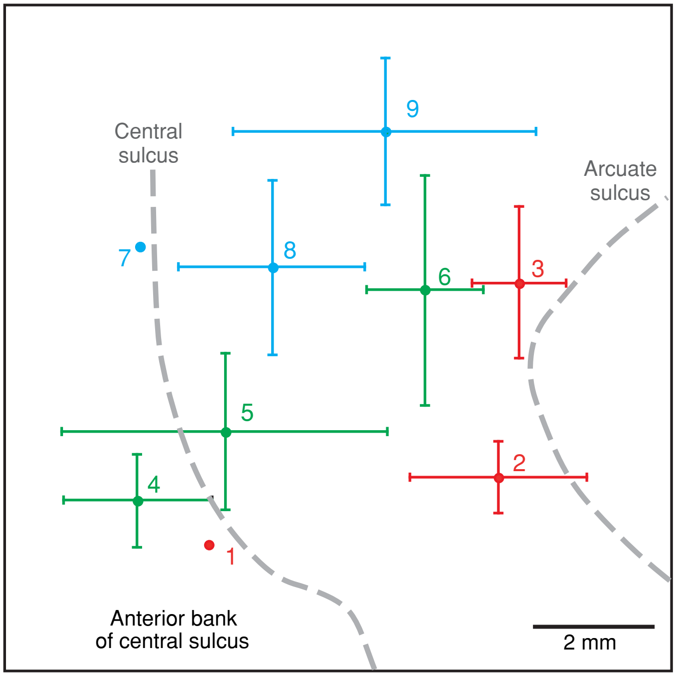

**Figure 6**

Map of stimulation-evoked hand locations in the precentral gyrus of an example monkey. The nine points show the mean location of cortical sites associated with nine spatial zones around the body. Upper space = red, mid-height space = green, lower space = blue. For definition of the nine zones, see **Figure 5*A***. Error bars = standard deviation showing scatter in the cortical location of the stimulation sites. For spatial zones represented by three or fewer stimulation sites, no error bars were plotted. These zones include zone 1 (N = 1) and zone 7 (N = 3). Dotted lines show location of lip of central sulcus and lip of arcuate sulcus. Area to the left of the lip of the central sulcus represents the anterior bank of the sulcus. Adapted from figure 4 of Graziano et al. 2003.

A third type of organization emerged from our stimulation results: the ethological organization described in the preceding sections in which specific movement categories are evoked from specific regions of cortex (**Figure 3**).

The three types of organization, (*a*) by somatotopy, (*b*) by the spatial location of the hand, and (*c*) by ethological function, are not fully compatible with each other. They conflict in specific instances, resulting in some disorder within each type of organization. For example, any complex, behaviorally relevant movement combines muscles from many parts of the body, effectively scrambling the somatotopic map. This noisy intermeshing of three different maps in one region of cortex suggested to us a possible dimensionality reduction. In this hypothesis, during the development or experience-dependent organizing of the map, the different mapping principles described above and possibly others compete for nearest neighbor relationships on the two-dimensional surface of the cortex, resulting in a fractured and somewhat multiply-organized region of cortex. Thus it is possible to discern each of these types of topographic organization in the data, but each one is noisy and statistical.

This multiplexed organization presents a problem to both splitters and lumpers. Does the lateral motor cortex fit within a single large map of the body, albeit a noisy one, such as Woolsey (1952) suggested? Is the arm and hand representation unified by a single rough map of hand position in space, such as we originally suggested (Graziano et al. 2002a,b)? Or is there a collection of separate cortical areas with fuzzy borders (e.g., Dum & Strick 2002, Preuss et al. 1996, Rizzolatti & Luppino 2001)? Both the splitters and lumpers may be correct. Our stimulation results suggest that subregions with distinct properties do exist but that they also fit into larger overarching organizations (something like the European Union).

## NEURONS IN MOTOR CORTEX MAY BE TUNED TO IDIOSYNCRATIC MOTOR OUTPUT PATTERNS

As described above, electrical stimulation of motor cortex can evoke complex, apparently meaningful movements. However, stimulation is a relatively crude probe, activating a ball of neural tissue around the electrode tip. How do single neurons in motor cortex encode movement?

Georgopoulos et al. (1986) studied monkeys performing a reaching task in which the hand started at a central location and moved to peripheral targets. They found that each neuron was broadly tuned to a preferred direction of reach. By averaging over a population of neurons it was possible to extract precise information about the direction of reach. Subsequent studies suggested that direction tuning may be only one part of a more complex tuning function. For most neurons, when the initial position of the hand was shifted to different parts of the workspace, or when the posture of the arm was altered, the preferred direction of reach changed (Caminiti et al. 1990; Scott & Kalaska 1995, 1997; Sergio & Kalaska 2003). Thus a single preferred direction of the hand in space could not account for the behavior of the neurons, and other variables such as joint angle and arm posture must have contributed. Neural correlates have been found for a range of variables including speed, force, joint angle, and muscle activity (e.g., Cheney et al. 1985, Evarts 1968, Georgopoulos et al. 1992, Holdefer & Miller 2002, Kakei et al. 1999, Li et al. 2001, Reina et al. 2001). It seems increasingly likely that the neurons are tuned to any combination of movement parameters that is useful to the animal.

Recently we examined neuronal tuning during a naturalistic and diverse set of arm movements (Aflalo & Graziano 2006). The monkey moved its limb freely, reaching for pieces of fruit, manipulating objects, putting items in its mouth, scratching and grooming itself, and engaging in other spontaneous behavior across the entire workspace of the arm. We measured the position of the hand in space, seven joint angles in the arm, and grip aperture. At the same time we recorded the activity of neurons in motor cortex. In this diverse and unconstrained movement set, the activity of the neuron was presumably influenced by many movement variables, and each variable was expected to contribute only a small percentage to the total variance. We asked how much of a neuron's variance could be attributed to direction tuning, tuning to a preferred final hand position, and tuning to a preferred final arm posture.

We first found that the direction-tuning model accounted for almost none of the variance in neuronal activity (**Figure 7*A***, black bars). For most neurons, the *r*-squared value obtained with the direction tuning model was less that 0.1. In our experiment, the movements involved a range of starting positions of the hand and starting postures of the arm. A neuron's directional tuning can change unpredictably when the starting position of the hand or the starting posture of the arm is changed (Caminiti et al. 1990; Scott & Kalaska 1995, 1997; Sergio & Kalaska 2003); therefore, we

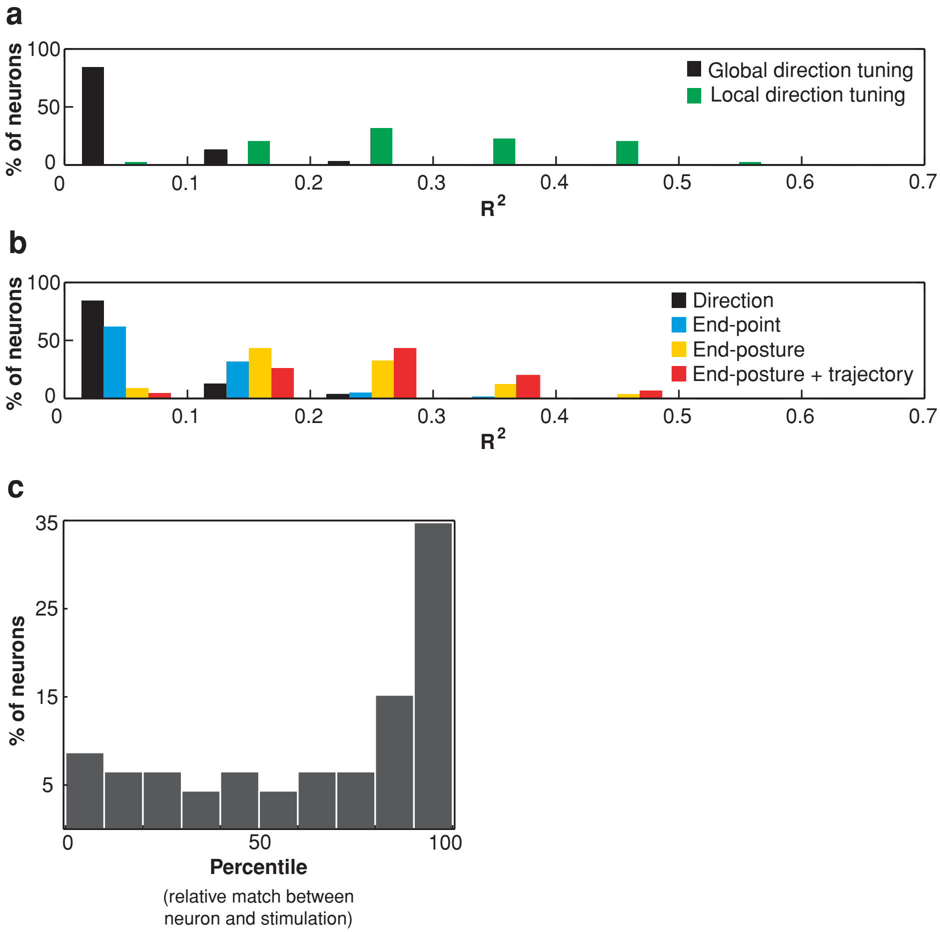

**Figure 7**

Single neurons in motor cortex are partially tuned to end posture. *A*: Frequency histogram of *r*-squared values obtained for 55 neurons. Black bars show *r*-squared values for a direction-tuning model (standard cosine tuning) tested over a diverse and naturalistic movement set. Green bars show *r*-squared values for a limited subset of movements that originated within a 5-cm radius sphere and were between 6 and 15 cm in length. *B*: Comparison of *r*-squared values obtained from motor cortex neurons using four different models. Direction-tuning model is the same as shown in *A*. In the preferred end-point model, firing rate was modeled as a Gaussian function of the position of the hand at the end of each movement, with the peak of the Gaussian located at the preferred end point. In the preferred end-posture model, firing rate was modeled as a Gaussian function of the end state of the arm in 8-dimensional posture space, with the peak of the Gaussian located at the preferred end-posture. In the preferred end-posture + trajectory model, an extra regressor was added to the end-posture model. In this posture + trajectory model, if the movement vector in eight-dimensional posture space was aimed directly at the preferred posture, the neuron fired more, and if the movement was aimed away from the preferred posture, the neuron fired less, with firing rate proportional to the cosine of the angular error. *C*: For each neuron, postures evoked by stimulation of all sites across motor cortex were ranked according to how well they matched the preferred posture for that neuron. Stimulation of the same cortical site as the neuron typically matched the neuron best, ranking between the 80th and 100th percentile.

did not expect to find a single preferred direction that could account for the neuron's activity. When we sorted through the monkey's recorded movements and selected a subset of movements that began at a similar location and extended a similar distance, approximating the limited center-out reaching task used by Georgopoulos et al. (1986), we obtained a significant degree of direction tuning (**Figure 7*A***, green bars). Thus the neurons appeared to be direction tuned over a limited, carefully selected set of movements. They were locally, but not globally, direction tuned.

Which tuning function, if any, could account for a cell's global behavior? We tested whether the neurons were tuned to a preferred position in space to which the hand moved. In this preferred-end-point model, a neuron should fire more during a movement that terminates near the preferred hand position and fire less during a movement that terminates far from the preferred hand position. For most neurons, this preferred-end-point model accounted for almost none of the variance in firing rate (**Figure 7 *B***, blue bars).

Finally we tested whether the neurons were tuned to a preferred end posture in the eight-dimensional (8-D) joint space of the arm. In this preferred-end-posture model, the neuron should fire more during a movement that terminates near the preferred posture and fire less during a movement that terminates far from the preferred posture, where "near" and "far" are defined by distance in 8-D joint space. This preferred-end-posture model provided a better match than did the preferred-direction or preferred-end-point models (**Figure 7*B***, yellow and red bars). Most neurons showed a significant degree of preference for movements that terminated near a specific posture. However, much of the variance remained unexplained even by the preferred-end-posture model. These results therefore do not show that neurons in motor cortex are primarily posture tuned. Rather, they show that the neurons have a significant component of tuning to end-posture but are presumably influenced by many other factors as well.

Further support for the partial tuning of neurons to a preferred end posture was obtained with electrical stimulation. Immediately after recording from a neuron, when we electrically stimulated the same cortical site through the same electrode, the arm was typically driven to a posture that closely matched the preferred posture of the neuron. A ranking analysis showed that a neuron's preferred posture was generally closer to the posture evoked by stimulation of the same cortical site than to the postures evoked by stimulation of other cortical sites (**Figure 7*C***). Although not all stimulation-evoked movements matched the single neuron properties, the match was statistically significant across the population. Thus in this experiment the correlational technique of single neuron recording converged with the causal technique of electrical stimulation to suggest a significant though limited component of end posture coding.

Our results suggest that direction tuning or any other single type of tuning may be too simple a model to account for the behavior of motor cortex neurons. Rather, the neurons may be hypertuned in a complex, multidimensional space, and some degree of tuning to single parameters can be extracted from that multidimensional tuning profile. Perhaps the significant component of end-posture tuning found here reflects the fact that monkeys spend a high proportion of time maintaining an arm posture to stabilize and orient the hand while the hand performs an action (Graziano et al. 2003). In this view, neurons in motor cortex are tuned to motor patterns that reflect the monkey's behavioral repertoire.

We hypothesize that the code for movement in motor cortex may be analogous to the code for visual object recognition that has been described in the inferior temporal (IT) cortex. Each neuron in IT cortex responds to a range of complex visual stimuli and has an idiosyncratic tuning function across those stimuli (Desimone et al. 1984). If any one stimulus parameter is systematically varied, such as orientation, size, color, position, or even the number of spokes radiating out of the stimulus, then most IT neurons will exhibit a smooth tuning curve along that parameter (Schwartz et al. 1983). These simple, one-dimensional tuning curves, however, do not capture the essential property, namely that the neurons are tuned to arbitrary complex patterns that are useful to the animal and that probably reflect the experience of the animal. For example, if an animal is overtrained to distinguish artificially created stimuli, then a disproportionate number of neurons in IT become tuned to those stimuli (Logothetis et al. 1995). Likewise, the disproportionate number of neurons tuned to faces probably reflects the importance of faces to the animal's behavior. We hypothesize that neurons in motor cortex may be tuned in a similar fashion to a vast set of motor patterns that may be entrained through experience and that may reflect the behavioral needs of the animal. In this view, the code is a population one as first suggested by Georgopoulos et al. (1986), but the basis set is idiosyncratic and constantly shifting through use.

## THE CORTICAL MAP OF MUSCLES IS CONTINUOUSLY REMAPPED BY FEEDBACK

The previous sections summarize the findings that electrical stimulation of motor cortex can produce complex postures that appear to reflect the monkey's behavioral repertoire and that single neurons in motor cortex are at least partially tuned to the same postures evoked by stimulation. The question arises how such complex properties can be represented in a cortical area that is relatively directly connected to the periphery. This section considers the possible connectional pattern between cortex and muscles and how this wiring may sustain complex motor behavior.

### One-to-One Mapping

**Figure 8*A*** shows a traditional view in which points in cortex map in a one-to-one fashion to muscles in the periphery. In this view, the spinal cord acts as a relay and does little or no processing of its own. This view of motor cortex was common in the early twentieth century (e.g., Foerster 1936, Fulton 1938). More recently, Asanuma and colleagues argued for a similar view (Asanuma 1975, Asanuma et al. 1976). Their work was based on brief, low-current stimulation of motor cortex and observation of the evoked movements. They found that by lowering the current to threshold, they could sometimes evoke a flexion or extension of a single joint, suggesting that only one muscle was stimulated. This work, however, left an alternative explanation. Each stimulation point in cortex could be connected to a range of muscles in a complex pattern of excitation and inhibition. Dropping the current to "threshold" would effectively reduce the output until only the strongest excitatory connection to a muscle would result in any visible movement. In this alternative view, Asanuma and colleagues may have been looking at the most active muscle in a complex, multimuscle ensemble.

**EMG:** electromyogram

Subsequent experiments supported this second, multimuscle hypothesis. When muscle activity was directly measured with electromyograms (EMG), electrical stimulation at a point in cortex was found to evoke a pattern of excitation and inhibition across a set of muscles that actuated many joints (Cheney et al. 1985; Donoghue et al. 1992; Park et al. 2001, 2004). Not just electrical stimulation of a point in cortex, but also the spiking of a single neuron in cortex, was correlated with increases and decreases in the activity of many muscles (Cheney & Fetz 1985, Holdefer & Miller 2002).

### Many-to-Many Mapping

**Figure 8*B*** shows a more modern view in which each cortical point connects to many muscles, and each muscle receives input from many cortical locations. This many-to-many connectivity is achieved because of the lateral

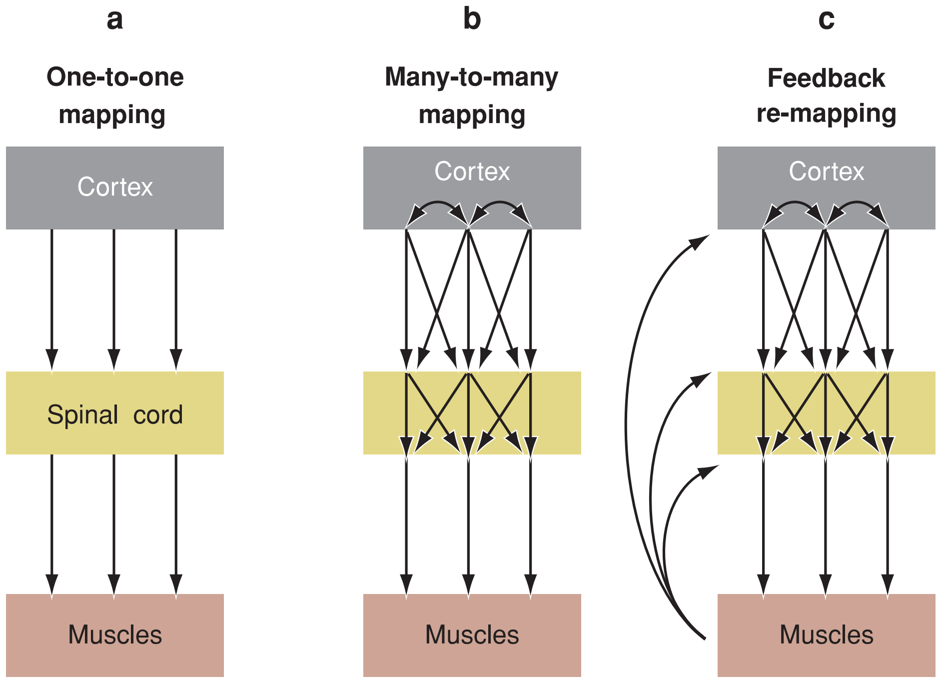

**Figure 8**

Three schematic wiring diagrams for the connectivity of cortex, spinal cord, and muscles. *A*: Traditional view of a one-to-one map in which the spinal cord acts as a relay. *B*: More complex view of a many-to-many map in which divergent connections and lateral connections allow each neuron in cortex to affect many muscles and each muscle to be affected by many cortical neurons. *C*: Architecture in which feedback from muscles and joints can change the specific mapping from cortical neurons to muscles. This feedback architecture allows for the control of a greater range of higher-order movement parameters.

connections and divergent projections at every stage in the pathway.

The lateral connections within cortex (e.g., Baker et al. 1998, Gatter et al. 1978, Ghosh & Porter 1988, Huntley & Jones 1991, Kwan et al. 1987, Matsumura et al. 1996) may contribute to the linking of different joints and body parts into more complex movements such as we find on electrical stimulation. Some of this functional linking of disparate sites in cortex has been studied recently in the cat motor cortex (Schneider et al. 2002).

Within the spinal cord, the interneuron circuitry can link different motoneuronal pools into larger units or muscle synergies (e.g., Bizzi et al. 2000, Jankowska & Hammer 2002). These muscle synergies have been studied particularly in the frog but appear to operate in mammals as well (e.g., d'Avella & Bizzi 2005, d'Avella et al. 2003, Hart & Giszter 2004, Krishnamoorthy et al. 2003, Ting & McPherson 2005). In this modular or muscle synergy view of spinal cord function, a neuron in cortex projecting downward to the spinal cord will not typically map to a single muscle in the periphery; rather, the cortical neuron will excite interneurons in the spinal cord and thus recruit muscle synergies. Some cortical neurons, especially those involved in the control of the fingers and wrist, project directly to the motoneuron pools in the spinal cord, bypassing the spinal interneurons (Bortoff & Strick 1993; Landgren et al. 1962; Lawrence 1994; Lemon et al. 1998, 2004; Maier et al. 1997, 2002; Murray & Colter 1981). Even in that case, the projections tend to be divergent, and thus it is unlikely that a single cortical neuron will map to a single muscle. Indeed neuronal recording studies suggest that, within the cortical representation of the fingers, each neuron can contribute to the control of more than one finger (Schieber 2002). Because animals do not generally need to contract individual muscles to perform any useful behavior, but rather need to contract muscles in specific, coordinated ensembles, why any level of the system should be organized to separate out the control of individual muscles is not clear. Thus, the view of a one-to-one map shown in **Figure 8*A*** is not generally accepted, and the view of a many-to-many map shown in **Figure 8*B*** is more commonly accepted (e.g., Cheney et al. 1985; Donoghue et al. 1992; Holdefer & Miller 2002; Park et al. 2001, 2004).

The architecture shown in **Figure 8*B***, however, is still fundamentally a linear and feed-forward one. In that architecture, each neuron in cortex ultimately affects a set of muscles, exciting some and inhibiting others in a fixed pattern.

## Feedback Remapping

The mapping from motor cortex to muscles can change gradually with experience (for a review see Sanes & Donoghue 2000). It is less well appreciated that the mapping can change instantaneously depending on feedback from the limb (Armstrong & Drew 1985, Graziano et al. 2004, Kakei et al. 1999, Lemon et al. 1995, Rho et al. 1999, Sanes et al. 1992). **Figure 8*C*** shows a diagram of an architecture that incorporates feedback.

**Figure 9*A*** shows an especially simple example of feedback remapping from a recent experiment (Graziano et al. 2004). Here we collected data from an anesthetized monkey whose elbow was fixed at several different angles. Stimulation pulses applied to a site in primary motor cortex resulted in a short latency activation of the triceps. The amount of triceps activation was modulated in a monotonic, roughly linear fashion by the angle at which the elbow joint was fixed. The more flexed the elbow was, the greater the evoked muscle activity was.

This experimental protocol probed a short-latency (~7 ms) neuronal pathway from the stimulated site in cortex to the muscle. The modulation caused by elbow angle occurred along this relatively direct pathway. The proprioceptive feedback could have modulated various steps along this pathway, such as altering the stimulation threshold of the neurons in cortex near the electrode tip, altering the circuitry within the spinal cord, or both. This example demonstrates that the wiring from a location in cortex to a muscle is not necessarily fixed but rather feedback dependent; the state of the limb can modulate the strength of the descending pathway.

This simple, seemingly trivial modulation by feedback may be used to construct arbitrarily complex codes for movement. One example is shown in **Figure 9*B***. Here again a point in primary motor cortex was stimulated. When the elbow was fully extended, stimulation caused short latency excitation of the biceps and little or no activity in the triceps. When the elbow was fully flexed, stimulation of the same site in cortex caused the opposite pattern, exciting the triceps and not the biceps. Essentially, that point in cortex was mapped to the biceps or to the triceps, switching back and forth depending on feedback about whether the elbow lay to one or the other side of a specific intermediate angle. Indeed, when this site in cortex was stimulated with an extended train of pulses, the elbow moved to that intermediate angle and then remained there. Thus, a relatively simple use of feedback can allow for the control of higher-order movement parameters, in this case a possible code for a goal elbow angle.

Another example of feedback remapping was provided by Kakei et al. (1999). They recorded from neurons in the motor cortex of monkeys performing a wrist movement task. For one type of neuron, if the forearm was supinated (palm up), activity of the neuron

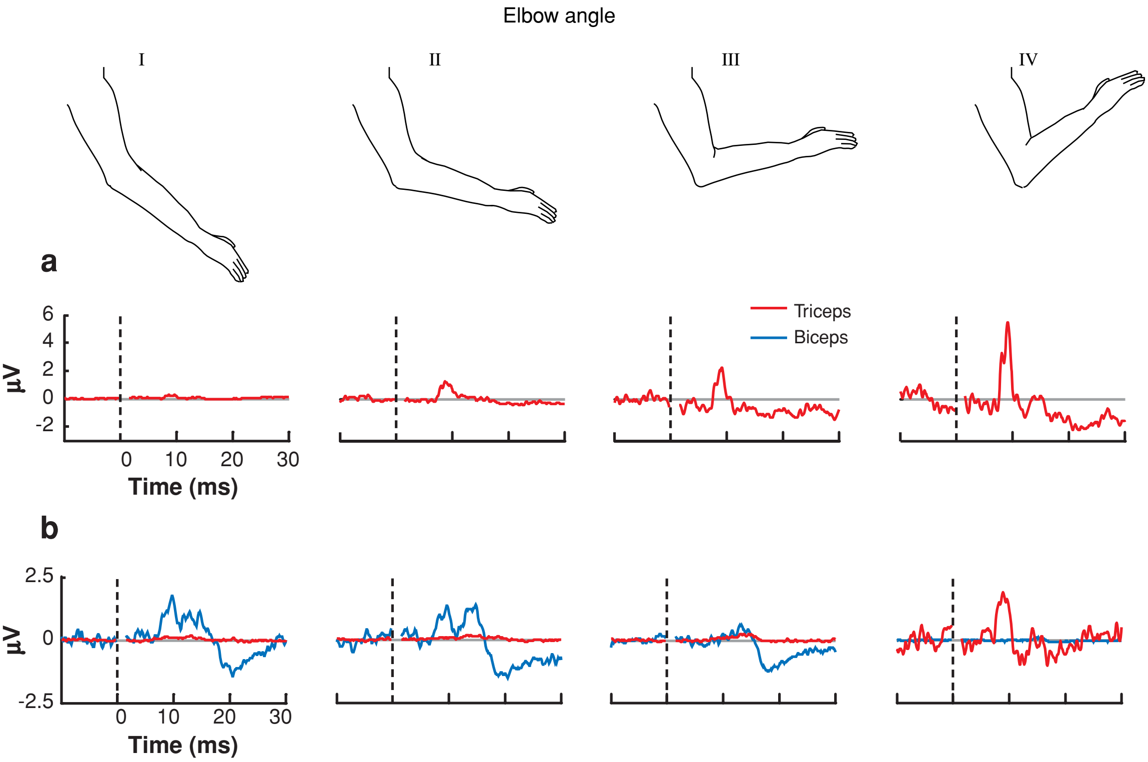

**Figure 9**

Cortico-muscle connectivity modulated by proprioceptive feedback. *Top*: The arm was fixed in four possible locations in an anesthetized monkey while biphasic stimulation pulses were applied to points in cortex (30 microamps, 15 Hz, 0.2 ms width per phase, negative phase leading). *A*: EMG activity in triceps evoked by stimulation of one point in primary motor cortex. Vertical line on each histogram indicates time of biphasic pulse delivered to brain (time from 0.2 ms before to 1.5 ms after the pulse is removed from the EMG data to avoid electrical artifact). Each histogram is a mean of 2000–4500 pulses. The stimulation-evoked activity was modulated by the angle of the joint. *B*: EMG activity in biceps and triceps evoked by stimulation of a second example point in primary motor cortex. Stimulation of this point in cortex could activate the biceps or the triceps depending on the angle of the joint. Adapted from Graziano et al. 2004.

was correlated with, and presumably helped to drive, the muscles that flex the wrist, resulting in the hand rotating upward. If the forearm was pronated (palm down), activity of the neuron was correlated with the muscles that extend the wrist, again resulting in the hand rotating upward. In this example, a single neuron in cortex encoded upward movement of the wrist regardless of the orientation of the limb. The underlying computation in this example is exactly the same as in the example in **Figure 9*B***. In both cases, a point in cortex was connected primarily to the flexors or to the extensors of a joint, depending on feedback about the angle of a joint. In the example from Kakei et al. (1999), the remapping resulted in a code for the direction of movement in extrinsic space. In the example in **Figure 9*B***, the remapping resulted in a code for a goal joint angle.

Feedback remapping could in principle be used to construct other complex codes for movement. Dynamic stretch receptors in the muscles detect the speed of joint rotation; receptors in the skin detect the pressure between the fingertips and an external object;

and receptors in the tendons detect the tension on muscles. These signals, feeding back into the spinal and cortical circuitry, could continuously remap the relationship between cortex and muscles, resulting in cortical neurons whose firing regulates any parameter or combination of parameters useful for movement. A feed-forward architecture, such as that in **Figure 8*A*** and ***B***, does not allow for this level of complexity. If motor cortex has a feed-forward architecture, then a higher-order brain area must be postulated that controls complex movements by playing on the muscle map in the motor cortex. A feedback architecture, such as that in **Figure 8*C***, can itself regulate and control complex actions.

## ACKNOWLEDGMENTS

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### SUMMARY POINTS

1. Motor cortex may be divisible into zones that emphasize different behaviorally relevant categories of movement. This ethological organization may intermesh with other, competing types of organization including a somatotopy and a map of hand location in space.
2. Single neurons in motor cortex may be tuned in an idiosyncratic fashion to complex, behaviorally useful patterns of motor output that reflect common actions in the monkey's repertoire. These tuning functions may include a significant component of end-posture tuning.
3. The connectivity between motor cortex and muscles is not fixed but fluid, changing constantly on the basis of feedback from the periphery. This feedback remapping may underlie the ability of the network to regulate almost any high-level or low-level movement parameter, flexibility needed to encode behaviorally relevant actions.

### FUTURE ISSUES TO BE RESOLVED

1. More extensive electrical stimulation experiments are needed to determine whether other cortical areas, such as the medial motor areas, show any specialization for specific classes of behavior. Stimulation experiments in other species may also help address the question of how closely the evoked movements reflect the behavioral repertoire of the animal.
2. The possible hierarchical organization, or lack thereof, among the cortical motor areas is not understood and requires more work directly comparing the properties of different areas.
3. Motor cortex cannot be understood without a better understanding of spinal function, including the complex feedback circuitry within the spinal cord, the intercoordination of muscles that cross many joints, and the experience-dependent adaptability of spinal circuits.

## LITERATURE CITED

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