9. FEEDBACK REMAPPING AND THE CORTICAL CONTROL OF MOVEMENT

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Abstract

Motor cortex in the primate brain controls movement at a complex level. For example, electrical stimulation of motor cortex on a behavioral time scale can elicit multi-joint movements that resemble common gestures in the monkey's behavioral repertoire. How is this complex control accomplished? It was once hypothesized that motor cortex contains a topographic, one-to-one map from points in cortex to muscles. It is now well known that the topography contains a considerable degree of overlap and that the mapping between points in cortex and muscles is many-to-many. However, can a fixed, many-to-many map account for the complex manner in which motor cortex appears to control movement? Recent experiments suggest that the mapping between cortex and muscles may be of a higher order than a fixed, many-to-many map; it may continuously change depending on proprioceptive feedback from the limb. This "feedback remapping" may be a fundamental aspect of motor control, allowing motor cortex to flexibly control almost any high-level or low-level aspect of movement.

Introduction

A central issue in the cortical control of movement is the nature of the map in motor cortex. Neurons in motor cortex map in some fashion to muscles in the periphery, but what are the properties of the map? Is the map one-to-one, in which each location in cortex projects to a single muscle? Is it many-to-many, in which each cortical point connects to many muscles, and each muscle receives input from many cortical locations? Is the map a fixed one, or does it change

depending on other sources of input that modulate the pathways between cortex and muscles?

Anatomically, primary motor cortex has a relatively direct, descending projection to the muscles. Pyramidal tract neurons in layer V of cortex project to the spinal cord, where they synapse onto spinal interneurons and in some cases directly onto motoneurons (He et al. 1993; Landgren et al. 1962; Lemon et al. 2004; Maier et al. 2002; Murray & Colter 1981). A range of studies suggest that the neuronal activity in motor cortex is tightly coupled to muscle output. For example, during voluntary movement, the activity of motor cortex neurons is correlated with muscle force and muscle activity (Evarts 1968; Holderfer & Miller 2002; Morrow & Miller 2003). The technique of "spike triggered averaging" shows that an action potential in a neuron in cortex can be followed at short latency by a transient change in muscle activity (Cheney & Fetz 1985; Fetz and Cheney 1980; Lemon et al. 1986; McKiernan et al. 1998). An electrical pulse applied to a point in motor cortex evokes a reliable, short latency effect in a specific set of muscles (Cheney et al. 1985; Maier et al. 1997; Olivier et al. 2001; Park et al. 2001). For these reasons, it appears that motor cortex exerts a relatively direct control over muscles.

The mapping from cortex to muscles, however, is not a punctate, one-to-one map as was once thought (Foerster 1936; Fulton 1938), but instead a many-to-many map (Donoghue et al. 1992; Gould et al. 1986; Jankowska et al. 1975; Kwan et al. 1978; Park et al. 2001; Sanes et al. 1995; Schieber & Hibbard 1993; Schneider et al. 2001). For example, the firing of a single neuron in cortex might be positively correlated with the activity of a set of homonymous muscles and negatively correlated with a set of antagonist muscles

(Cheney & Fetz 1985). This functional linking of a single cortical neuron to many muscles may occur at a variety of levels. It may be partly the result of lateral connections within motor cortex (Baker et al. 1998; Capaday et al. 1998; Gatter et al. 1978; Ghosh & Porter 1988; Huntley & Jones 1991; Kang et al. 1988; Kwan et al. 1987; Landry et al. 1980; Matsumura et al. 1996; Schneider et al. 2002); partly the result of the divergent projection from single neurons in the cortex to multiple target neurons in the spinal cord (Asanuma et al. 1979; Kuang & Kalil 1990; Shinoda et al. 1976); and partly the result of the propriospinal and other interneurons within the spinal cord that link the control of different muscles into functionally useful groups (Bizzi et al. 2000; Jankowska and Hammer 2002; Tantisira et al. 1996). This complexity at every level of the pathway from cortex to muscle results in the many-to-many mapping in which each cortical neuron influences many muscles and each muscle is influenced by many cortical neurons.

One hypothesis is that a fixed, many-to-many mapping from cortex to muscles provides an essentially accurate description of the system, and furthermore can explain how the motor cortex controls movement in such a complex manner. Neurons in motor cortex are active in correlation with a range of movement parameters including direction of movement of the hand through space, velocity, force, joint angle, and arm posture (e.g. Evarts 1968; Caminiti et al. 1990; Georgopoulos et al. 1986; Georgopoulos et al. 1989; Kakei et al. 1999; Kalaska et al. 1989; Reina et al. 2001; Scott & Kalaska 1995; Scott & Kalaska 1997; Sergio & Kalaska 2003). Stimulation of motor cortex on a behavioral time scale can evoke complex, multijoint movements that appear to match the monkey's normal behavioral repertoire (Cooke & Graziano 2004; Graziano et al. 2002a,b; Graziano et al. 2004). Can such complex, higher-order control of movement have as its basis a fixed, many-to-many map from cortex to muscles? One model of cortical function (Todorov 2000) shows that a surprising range of movement parameters can indeed be controlled through a many-to-many muscle map, once the physical properties of the muscles are taken into account.

However, a fixed, many-to-many mapping from cortex to muscles may be an oversimplification. A variety of results suggest that the mapping from cortical neurons to muscles may change from moment to moment, depending on feedback information regarding the kinematic state of the limb (Armstrong & Drew 1985; Bennett & Lemon 1994; Graziano et al. 2004; Kakei et al. 1999; Lemon et al. 1995; Rho et al. 1999; Sanes et al. 1992). Proprioceptive signals from the periphery reach the spinal cord and the cortex, and thus are in a position to modulate the flow of information

from neurons in cortex to the muscles. The firing of an output neuron in motor cortex therefore might have very different consequences, resulting in very different patterns of muscle activation, depending on the kinematic state of the limb. In this hypothesis, the mapping from cortical neurons to muscles may not be fixed, but rather may be continuously remapped.

Feedback remapping might allow for a reconciliation between two views of motor cortex. The first view is that there is a direct mapping from the cortical output neurons to the muscles (e.g. Asanuma 1975; Cheney et al. 1985; Evarts 1968; Holderfer & Miller 2002; Lemon et al. 1986). The second view is that motor cortex neurons control high-level movement parameters (Caminiti et al. 1990; Georgopoulos et al. 1986; Georgopoulos et al. 1989; Kakei et al. 1999; Kalaska et al. 1989; Reina et al. 2001). This debate has sometimes been termed the "muscles vs movements" debate. The view of feedback remapping is that there is indeed a mapping from cortex to muscles, but that the mapping is continually adjusted on the basis of kinematic feedback, thereby providing the flexibility to control almost any high-level or low-level aspect of movement.

In this view, feedback remapping is a more fundamental principle than any specific movement coding scheme. Finding the "correct" coding scheme by which motor cortex controls movement, determining whether that scheme is a velocity code, a force code, a direction code, or a postural code, may be misguided, since different tasks might require the control and optimization of different movement parameters (Todorov & Jordan, 2002).

Examples of Feedback Remapping

Sanes et al. (1992) provided one of the first demonstrations of proprioceptive feedback changing the mapping between motor cortex and muscles. They used intracortical microstimulation to map motor cortex in the rat, and found that by placing the rat's forelimb in different postures they could alter the apparent map of muscles in cortex. For example, when the forelimb was in an extended posture, the biceps representation in cortex was enlarged. When the forelimb was in a flexed posture, the biceps representation in cortex shrank. This type of change in the cortical representation of muscles due to proprioceptive feedback has been obtained in many experiments in humans, monkeys, and cats (Armstrong & Drew 1985; Bennett & Lemon 1994; Graziano et al. 2004; Lemon et al. 1995; Rho et al. 1999).

Figure 1A shows an example from a recent experiment (Graziano et al. 2004) in which proprioceptive information about the angle of the elbow joint altered
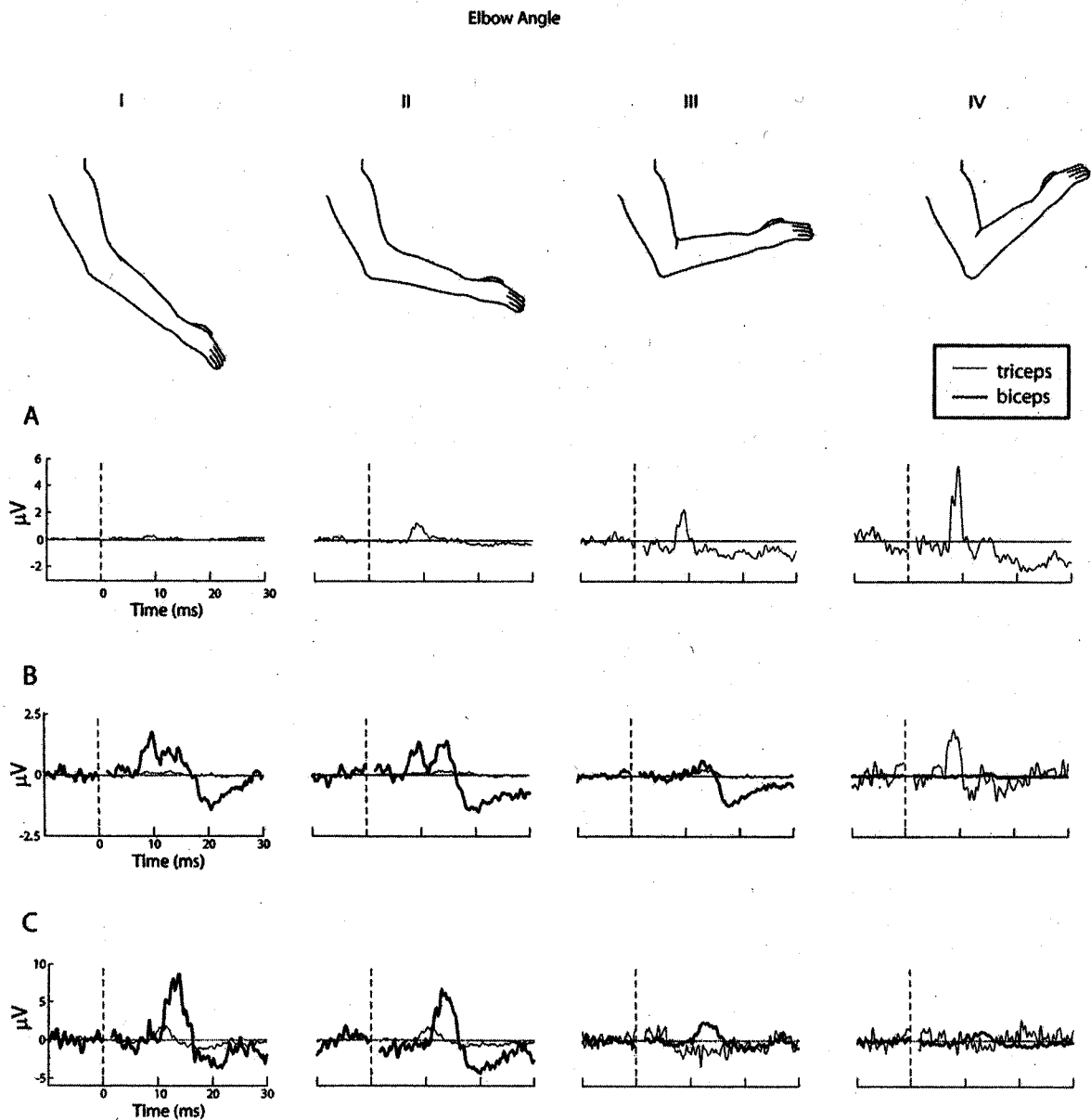
FIGURE 1. Cortico-muscle connectivity modulated by proprioceptive feedback. Top: The arm was fixed in four possible locations in an anesthetized monkey while biphasic stimulation pulses were applied to points in cortex (30 microamps, 15 Hz, 0.2 ms width per phase, negative phase leading). Electromyographic (EMG) activity was recorded in biceps and triceps. 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. Thus the effective connection strength between the stimulated point in cortex and the muscle was modulated by joint angle. 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. One interpretation is that activity at that location in cortex signals the elbow to move from any initial angle toward an intermediate, final angle. When the elbow is more flexed than the desired final angle, stimulation evokes mainly triceps activity. When the elbow is more extended than the desired final angle, stimulation evokes mainly biceps activity. C. EMG activity in biceps and triceps evoked by stimulation of a third example point in primary motor cortex. Stimulation of this point in cortex activated primarily the biceps. One interpretation is that activity at that location in cortex signals the elbow to move in a controlled fashion toward flexion. When the elbow is far from a flexed position, stimulation evokes a higher level of biceps activity and a greater discrepancy between biceps and triceps activity. When the elbow is near full flexion, stimulation evokes a lower level of biceps activity and a smaller discrepancy between biceps and triceps activity.

the effective connectivity between a point in cortex and the triceps. Here we collected data from an anesthetized monkey whose elbow was fixed at several different angles. Stimulation pulses applied to this site in cortex resulted in a short latency activation of the triceps. The amount of triceps activation was modulated in a simple, monotonic, roughly linear fashion by the angle at which the elbow joint was fixed. The more flexed the elbow, the greater the evoked muscle activity.

It is important to note that the change in evoked activity in the triceps was not a result of a length/tension relationship, in which muscle tension varies with muscle length due to the physical properties of the muscle. Here we were not measuring the evoked tension in the muscle, but the evoked electromyographic activity.

It is also important to note that, by using the technique of stimulus triggered averages (Cheney et al. 1985), the experiment was able to probe a short-latency (approximately 7 ms) neuronal pathway from the stimulated site in cortex to the muscle. The modulation caused by elbow angle must have 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. For example, stretch receptors in the biceps and triceps might have fed back to the spinal cord and altered the excitability of the alpha motor neuron pool for the triceps.

The example in Figure 1A represents a relatively simple building block, a cortico-muscle connection that is modulated in a monotonic, roughly linear fashion by joint angle. In the following sections we discuss how this simple building block might be used to control highly complex movement parameters.

Remapping a Point in Cortex from Flexor to Extensor

Figure 1B shows an example in which a point in motor cortex was remapped from the biceps to the triceps when the elbow angle was changed (Graziano et al. 2004). Here we stimulated a point in motor cortex and found a short-latency excitatory response in both the biceps and triceps. When the elbow was fixed in an extended posture, activity at that point in cortex excited the biceps more than the triceps. When the elbow was fixed in a flexed posture, activity at that point in cortex excited the triceps more than the biceps. Essentially, this point in cortex could be functionally connected to the flexors or to the extensors depending on the angle of the elbow.

Our interpretation in the present example is that the pattern of activity is designed to initiate movement of the elbow toward an intermediate, goal angle, regardless of the starting angle. When the arm is initially extended, the increase in biceps activity should initiate a flexion. When the arm is initially flexed, the increase in triceps activity should initiate an extension. Indeed, when this site in cortex was stimulated with a 400-ms train of pulses presented at 200 Hz, and the arm was free to move, the elbow moved to a partially flexed angle regardless of its starting angle and then remained at that final posture until the end of the stimulation train.

In this interpretation, the output neurons at the stimulated site in cortex did not encode a specific pattern of muscle activity; instead, they encoded movement to a desired posture. Thus a fundamentally muscle-based map, with the addition of a simple feedback remapping rule, can in principle be used to construct a higher-order, postural code for movement.

Movement to an Extreme Angle

As described above, for some sites in cortex, stimulation can result in movement of a joint to a goal angle. For other sites, however, stimulation results in movement of a joint in one direction only. If such a site in cortex is stimulated for a long enough duration, the joint reaches an extreme position. This type of site was classically described with respect to the control of the fingers (Asanuma 1975). This pattern of results was interpreted as evidence of a relatively direct, fixed connection between the stimulated point in cortex and a single muscle, either a flexor or an extensor. However, even in this case, the mapping between cortex and muscle may not be simple or fixed and may be modulated by proprioceptive feedback.

Figure 1C shows an example of a site in cortex that when stimulated always drove the elbow toward flexion (Graziano et al. 2004). The evoked muscle activity was nonetheless modulated by joint angle. In this case, the strength of the cortico-biceps pathway was greatest when the elbow was fully extended and least when the elbow was fully flexed. The discrepancy between biceps and triceps activity was also greatest the elbow was extended and least when the elbow was flexed.

The practical effect of this modulation is that activity at this site should initiate a regulated movement of the elbow toward flexion, in which the amount of muscle activity depends on how far the elbow must be moved to reach full flexion. In this interpretation, the output neurons at the stimulated point in cortex did

not encode a fixed pattern of muscle activity. Instead, they encoded a regulated *movement* toward flexion in which different patterns of muscle activity might be required under different circumstances. At other stimulation sites, for which stimulation resulted in an extension of the elbow, a corresponding result was obtained with respect to the triceps.

Feedback Remapping and the Coding of Movement Direction

In principle, the same mechanism of feedback remapping outlined above could allow proprioceptive feedback from one joint to modulate the connections between cortex and the muscles that cross a different joint. In this way, the movement or position of one joint could interact with the cortical control of another joint. One example of this type 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 some neurons, the orientation of the forearm remapped the relationship between neuronal activity and the muscles that actuate the wrist. For example, for one type of neuron, if the forearm was supinated (palm up), activity of the neuron 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 is the same as in the example in Figure 1B. In both cases, a point in cortex was connected primarily to the flexors or to the extensors depending on feedback about the angle of a joint. In the example from Kakei et al., the remapping resulted in a code for direction of movement in extrinsic space.

Feedback remapping could in principle be used to construct other complex codes for movement as well. For example, dynamic stretch receptors in the muscles detect the speed of joint rotation, and therefore could modulate the mapping from cortex to muscles on the basis of velocity, resulting in a movement code in which neurons in cortex help to specify the velocity of the movement (e.g. Reina et al. 2001). Feedback remapping could also result in combinations of different types of coding, in which aspects of posture, direction, and speed are all controlled to some degree to result in a complex action. Such actions that appear to combine the control of many different parameters

are reminiscent of the movements evoked by electrical stimulation of motor cortex, such as bringing the hand to the mouth in an apparently speed-controlled manner (Graziano et al. 2002a,b).

Summary

A traditional debate in motor physiology is whether motor cortex controls behavior at the level of movements or of muscles (Taylor & Gross 2003). Neurons in motor cortex become active in correlation with many movement parameters such as direction of movement of the hand through space, velocity, force, joint angle, and arm posture (e.g. Caminiti et al. 1990; Evarts 1968; Georgopoulos et al. 1986; Georgopoulos et al. 1989; Kakei et al. 1999; Kalaska et al. 1989; Reina et al. 2001; Scott& Kalaska 1995; Scott & Kalaska 1997; Sergio & Kalaska 2003). Electrical stimulation of motor cortex on a behavioral time scale results in complex, multijoint movements that appear to match the monkey's normal behavioral repertoire (Cooke & Graziano 2004; Graziano et al. 2002a,b; Graziano et al. 2004). Even purely spatial information separated from any overt movement can influence neurons in motor cortex (Crowe et al. 2004). It is therefore clear that motor cortex is not simply a topographic map of muscles. Yet it does have a relatively direct, descending pathway to the muscles, and neurons in motor cortex are highly correlated with muscle output (Cheney et al. 1985; Evarts 1968; He et al. 1993; Holdefer & Miller 2002; Lemon et al. 1986). Perhaps the relevant question is not whether motor cortex controls muscles or movements, since it clearly does both. Rather, the relevant question may be: what are the variables that intervene between motor cortex and muscles?

Here we emphasize that proprioceptive feedback from the limb is an important class of variables that intervenes between motor cortex and muscles. In this view, motor cortex is mapped to muscles, and this mapping can be changed on a moment-by-moment basis as a result of feedback from joint angle and muscle stretch. We propose that this feedback remapping provides tremendous processing power and can underlie the cortical control of both simple and complex motor variables, such as when activity in cortex specifies a flexion or extension of a joint, a goal angle for a joint, a movement in a particular direction in space, or a movement of a particular peak speed. We suggest that feedback remapping may be an overarching method of motor control that can be used to construct many different, specific motor coding schemes. These specific motor coding schemes might depend on the subregion of motor cortex under study, the body part being

controlled, the task being performed by the animal, or the training history of the animal.

References

Armstrong DM, Drew T (1985) Forelimb electromyographic responses to motor cortex stimulation during locomotion in the cat. J Physiol 367: 327–351.

Asanuma H (1975) Recent developments in the study of the columnar arrangement of neurons within the motor cortex. Physiol Rev 55: 143–156.

Asanuma H, Zarzecki P, Jankowska E, Hongo T, Marcus S (1979) Projection of individual pyramidal tract neurons to lumbar motor nuclei of the monkey. Exp Brain Res 34: 73–89.

Baker SN, Olivier E, Lemon RN (1998) An investigation of the intrinsic circuitry of the motor cortex of the monkey using intra-cortical microstimulation. Exp Brain Res 123: 397–411.

Bennett KM, Lemon RN (1994) The influence of single monkey cortico-motoneuronal cells at different levels of activity in target muscles. J Physiol 477: 291–307.

Bizzi E, Tresch MC, Saltiel P, d'Avella A (2000) New perspectives on spinal motor systems. Nat Rev Neurosci 1: 101–108.

Caminiti R, Johnson PB, Urbano A (1990) Making arm movements within different parts of space: dynamic aspects in the primate motor cortex. J Neurosci 10: 2039–2058.

Capaday C, Devanne H, Bertrand L, Lavoie BA (1998) Intracortical connections between motor cortical zones controlling antagonistic muscles in the cat: a combined anatomical and physiological study. Exp Brain Res 120: 223–232.

Cheney PD, Fetz EE (1985) Comparable patterns of muscle facilitation evoked by individual corticomotoneuronal (CM) cells and by single intracortical microstimuli in primates: evidence for functional groups of CM cells. J Neurophys 53: 786–804.

Cheney PD, Fetz EE, Palmer SS (1985) Patterns of facilitation and suppression of antagonist forelimb muscles from motor cortex sites in the awake monkey. J Neurophys 53: 805–820.

Cooke DF, Graziano MSA (2004) Sensorimotor integration in the precentral gyrus: polysensory neurons and defensive movements. J Neurophys 91: 1648–1660.

Crowe DA, Chafee MV, Averbeck BB, Georgopoulos AP (2004) Participation of primary motor cortical neurons in a distributed network during maze solution: representation of spatial parameters and time-course comparison with parietal area 7a. Exp Brain Res 158: 28–34.

Donoghue JP, LeiBovic S, Sanes JN (1992) Organization of the forelimb area in squirrel monkey motor cortex: representation of digit, wrist, and elbow muscles. Exp Brain Res 89: 1–19.

Evarts EV (1968) Relation of pyramidal tract activity to force exerted during voluntary movement. J Neurophys 31: 14–27.

Fetz EE, Cheney PD (1980) Postspike facilitation of forelimb muscle activity by primate corticomotoneuronal cells. J Neurophys 44: 751–772.

Foerster O (1936) The motor cortex of man in the light of Hughlings Jackson's doctrines. Brain 59: 135–159.

Fulton JF (1938) Physiology of the Nervous System. Oxford University Press, New York, p. 399–457.

Gatter KC, Sloper JJ, Powell TP (1978) The intrinsic connections of the cortex of area 4 of the monkey. Brain 101: 513–541.

Georgopoulos AP, Schwartz AB, Kettner RE (1986) Neuronal population coding of movement direction. Science 233: 1416–1419.

Georgopoulos AP, Lurito JT, Petrides M, Schwartz AB, Massey JT (1989) Mental rotation of the neuronal population vector. Science 243: 234–236.

Ghosh S, Porter R (1988) Morphology of pyramidal neurones in monkey motor cortex and the synaptic actions of their intracortical axon collaterals. J Physiol 400: 593–615.

Gould HJ 3rd, Cusick CG, Pons TP, Kaas JH (1986) The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. J Comp Neurol 247: 297–325.

Graziano MSA, Taylor CSR, Moore T (2002) Complex movements evoked by microstimulation of precentral cortex. Neuron 34: 841–851.

Graziano MSA, Taylor CSR, Moore T, Cooke DF (2002) The cortical control of movement revisited. Neuron 36: 349–362.

Graziano MSA, Patel KT, Taylor CSR (2004) Mapping from motor cortex to biceps and triceps altered by elbow angle. J Neurophys 92: 395–407.

He SQ, Dum RP, Strick PL (1993) Topographic organization of corticospinal projections from the frontal lobe: motor areas on the lateral surface of the hemisphere. J Neurosci 13: 952–980.

Holdefer RN, Miller LE (2002) Primary motor cortical neurons encode functional muscle synergies. Exp Brain Res 146: 233–243.

Huntley GW, Jones EG (1991) Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: a correlative anatomic and physiological study. J Neurophys 66: 390–413.

Jankowska E, Hammar I (2002) Spinal interneurones; how can studies in animals contribute to the understanding

of spinal interneuronal systems in man? Brain Res Rev 40:19–28.

Jankowska E, Padel Y, Tanaka R (1975) The mode of activation of pyramidal tract cells by intracortical stimuli. J Physiol 249: 617–636.

Kakei S, Hoffman D, Strick P (1999) Muscle and movemet representations in the primary motor cortex. Science 285: 2136–2139.

Kalaska JF, Cohen DA, Hyde ML, Prud'homme MA (1989) Comparison of movement direction-related versus load direction-related activity in primate motor cortex, using a two-dimensional reaching task. J Neurosci 9: 2080–2102.

Kang Y, Endo K, Araki T (1988) Excitatory synaptic actions between pairs of neighboring pyramidal tract cells in the motor cortex. J Neurophys 59: 636–647.

Kuang RZ, Kalil K (1990) Branching patterns of corticospinal axon arbors in the rodent. J Comp Neurol 292: 585–598.

Kwan HC, MacKay WA, Murphy JT, Wong YC (1978) Spatial organization of precentral cortex in awake primates. II. Motor outputs. J Neurophys 41: 1120–1131.

Kwan HC, Murphy JT, Wong YC (1987) Interaction between neurons in precentral cortical zones controlling different joints. Brain Res 400: 259–269.

Landgren S, Phillips CG, Porter R (1962) Cortical fields of origin of the monosynaptic pyramidal pathways to some alpha motoneurones of the baboon's hand and forearm. J Physiol 161: 112–125.

Landry P, Labelle A, Deschenes M (1980) Intracortical distribution of axonal collaterals of pyramidal tract cells in the cat motor cortex. Brain Res 191: 327–336.

Lemon RN, Johansson RS, Westling G (1995) Corticospinal control during reach, grasp, and precision lift in man. J Neurosci 15: 6145–6156.

Lemon RN, Kirkwood PA, Maier MA, Nakajima K, Nathan P (2004) Direct and indirect pathways for corticospinal control of upper limb motoneurons in the primate. Prog Brain Res 143: 263–279.

Lemon RN, Mantel GW, Muir RB (1986) Corticospinal facilitation of hand muscles during voluntary movement in the conscious monkey. J Physiol 381: 497–527.

Maier MA, Armand J, Kirkwood PA, Yang HW, Davis JN, Lemon RN (2002) Differences in the corticospinal projection from primary motor cortex and supplementary motor area to macaque upper limb motoneurons: an anatomical and electrophysiological study. Cereb Cortex 12: 281–296.

Maier MA, Olivier E, Baker SN, Kirkwood PA, Morris T, Lemon RN (1997) Direct and indirect corticospinal control of arm and hand motoneurons in the squirrel monkey (Saimiri sciureus). J Neurophys 78: 721–733.

Matsumura M, Chen D, Sawaguchi T, Kubota K, Fetz EE (1996) Synaptic interactions between primate precentral cortex neurons revealed by spike-triggered averaging of intracellular membrane potentials in vivo. J Neurosci 16: 7757–7767.

McKiernan BJ, Marcario JK, Karrer JH, Cheney PD (1998) Corticomotoneuronal postspike effects in shoulder, elbow, wrist, digit, and intrinsic hand muscles during a reach and prehension task. J Neurophys 80: 1961–1980.

Murray EA, Coulter JD (1981) Organization of corticospinal neurons in the monkey. J Comp Neurol 195: 339–365.

Morrow MM, Miller LE (2003) Prediction of muscle activity by populations of sequentially recorded primary motor cortex neurons. J Neurophys 89: 2279–2288.

Olivier E, Baker SN, Nakajima K, Brochier T, Lemon RN (2001) nvestigation into non-monosynaptic corticospinal excitation of macaque upper limb single motor units. J Neurophys 86: 1573–1586.

Park MC, Belhaj-Saif A, Gordon M, Cheney PD (2001) Consistent features in the forelimb representation of primary motor cortex in rhesus macaques. J Neurosci 21: 2784–2792.

Reina GA, Moran DW, Schwartz AB (2001) On the relationship between joint angular velocity and motor cortical discharge during reaching. J Neurophys 85: 2576–2589.

Rho MJ, Lavoie S, Drew T (1999) Effects of red nucleus microstimulation on the locomotor pattern and timing in the intact cat: a comparison with the motor cortex. J Neurophys 81: 2297–2315.

Sanes JN, Donoghue JP, Thangaraj V, Edelman RR, Warach S (1995) Shared neural substrates controlling hand movements in human motor cortex. Science 268: 1775–1777.

Sanes JN, Wang J, Donoghue JP (1992) Immediate and delayed changes of rat cortical output representation with new forelimb configurations. Cereb Cortex 2: 141–152.

Schieber MH, Hibbard LS (1993) How somatotopic is the motor cortex hand area? Science 261: 489–492.

Schneider C, Devanne H, Lavoie BA, Capaday C (2002) Neural mechanisms involved in the functional linking of motor cortical points. Exp Brain Res 146: 86–94.

Schneider C, Zytnicki D, Capaday C (2001) Quantitative evidence for multiple widespread representations of individual muscles in the cat motor cortex. Neurosci Lett 310: 183–187.

Scott SH, Kalaska JF (1995) Changes in motor cortex activity during reaching movements with similar hand paths but different arm postures. J Neurophys 73: 2563–2567.

Scott SH, Kalaska JF (1997) Reaching movements with similar hand paths but different arm orientations. I. Activity

of individual cells in motor cortex. J Neurophys 77: 826–852.

Sergio LE, Kalaska JF (2003) Systematic changes in motor cortex cell activity with arm posture during directional isometric force generation. J Neurophys 89: 212–228, 2003.

Shinoda Y, Arnold AP, Asanuma H (1976) Spinal branching of corticospinal axons in the cat. Exp Brain Res 26: 215–234.

Shinoda Y, Yamaguchi T, Futami T (1986) Multiple axon collaterals of single corticospinal axons in the cat spinal cord. J Neurophys 55: 425–448.

Tantisira B, Alstermark B, Isa T, Kummel H, Pinter M (1996) Motoneuronal projection pattern of single C3-C4

propriospinal neurones. Can J Physiol Pharmacol 74: 518–530.

Taylor CSR, Gross, CG (2003) Twitches vs. Movements: a story of motor cortex. Neuroscientist 9: 332–342.

Todorov E (2000) Direct cortical control of muscle activation in voluntary arm movements: a model. Nat Neurosci 3: 391–398.

Todorov E, Jordan MI (2002) Optimal feedback control as a theory of motor coordination. Nat Neurosci 5: 1226–1235.

Weiss DS, Keller A (1994) Specific patterns of intrinsic connections between representation zones in the rat motor cortex. Cereb Cortex 4: 205–214.