

# The Integrated Nature of Motor Cortical Function

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Recent studies on the functional organization and operational principles of motor cortical function, taken together, strongly support the notion that the motor cortex controls the muscle activities subserving movements in an integrated manner. For example, during pointing the shoulder, elbow and wrist muscles appear to be controlled as a coupled functional system, rather than individually and separately. The pattern of intrinsic connections between motor cortical points is likely part of the explanation of this operational principle. So too is the manner in which muscles and muscle synergies are represented in the motor cortex. However, selection of movement-related muscle synergies is likely a dynamic process involving the functional linking of a variety of motor cortical points, rather than the selection of fixed patterns embedded in the motor cortical circuitry. One of the mechanisms that may be involved in the functional linking of motor cortical points is disinhibition. Thus, motor cortical points are recruited into action by selected excitation as well as by selected release from inhibition. The incoordination of limb movements in patients after a stroke may be understood, at least in part, as a disruption of the connections between motor cortical points and of the neural mechanisms involved in their functional linking. *NEUROSCIENTIST* 10(3):207–220, 2004. DOI: 10.1177/107385403262109

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*He [Sherrington] recorded only the proven, the verified thesis. In this he differed greatly from Hughlings Jackson whose printed hypothetical surmise ranged always far beyond the possibility of immediate proof. Sherrington was a scientist; Jackson was an observer and philosopher.*

—Penfield and Rasmussen (1950)

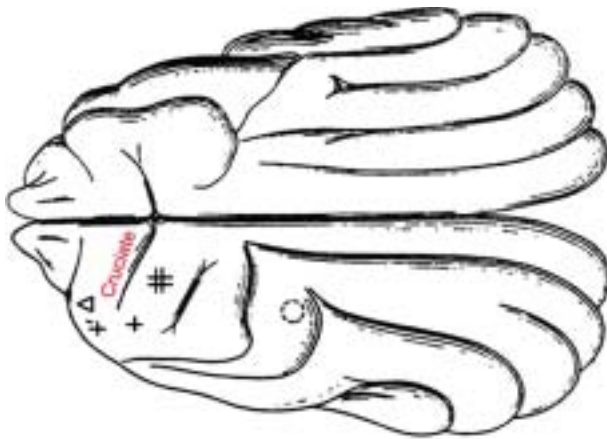
Since its discovery by Fritsch and Hitzig (1870) experimentally and inferred by Jackson (1868)\* on the basis of clinical observations, the motor cortex has been one of the most extensively studied areas of the mammalian brain (Fig. 1). Together with Paul Broca's (1861) discovery of a language center in the left hemisphere of the cerebral cortex, the demonstration of a cortical motor center put an end to the doctrine (Flourens 1842) that function was widely distributed across the cerebral cortex (i.e., not localized; see Schafer's [1900] historical account). The motor cortex is not the locus of motor command decision. It is, rather, as I will develop in this article, the motor command synthesizer and dispatcher.

\*Note the original cited references to Hughlings-Jackson may be found in the two volumes set "Selected writings" published in 1931. An excellent summary of his ideas on the organization and function of the motor cortex is in the paper titled "Some implications of dissolution of the nervous system" ("Selected writings" vol. II, p. 29).

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That is, once a decision to move is made, the motor cortex synthesizes the movement commands and relays them to the motor centers of the brainstem and spinal cord. However, the functional organization, neural circuitry, and operational principles of motor cortical function are far from understood, but significant advances have recently been made and are the subject matter of this review.

At the outset, the highly insightful British neurologist Hughlings Jackson (1882) thought of the motor cortex as an integrative cortical structure representing movements, not individual muscles. In the intervening decades, the pendulum of scientific perspectives swung toward the view that muscles are represented in the motor cortex. In particular, the detailed motor cortical maps of great apes derived by Leyton and Sherrington (1917) led to the punctate localization theory. The essence of this idea is that the motor cortex is composed of a mosaic of points, each representing a small flick-like movement or activating two muscles reciprocally. The function of the motor cortex according to Leyton and Sherrington (1917) was to synthesize these simple fractional components into the combinations required for coordinated movements. A notable opponent to the punctate localization theory was F. M. R. Walshe (1943). He elegantly argued in his essay that the experimental and clinical data available at the time were best interpreted by considering the motor cortex as representing complex patterns of overlapping and graded movement representations. Like Jackson, he thought that



**Fig. 1.** Fritsch and Hitzig's original 1870 drawing of the "excitable" area of the dog's cerebral cortex. I have labeled the cruciate sulcus in red. The symbols (+, #, etc.) indicate points around the cruciate sulcus from which movements could be evoked by electrical stimulation. Hitzig went on to publish one more seminal paper in 1874 on the simian motor cortex before devoting the rest of his life to adventures in foreign travel.

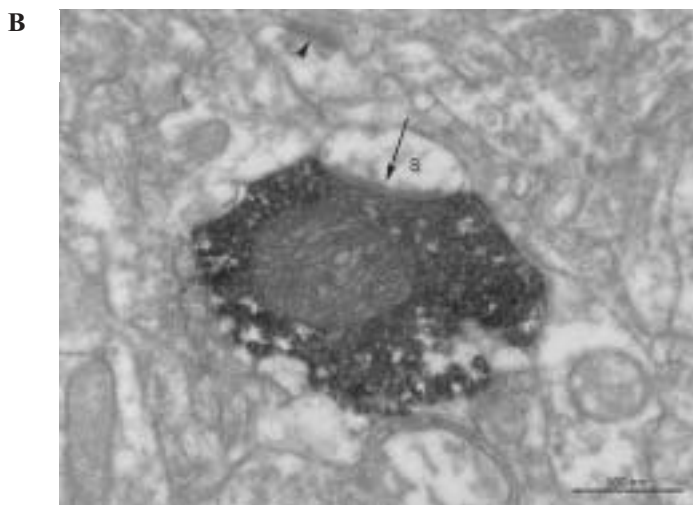
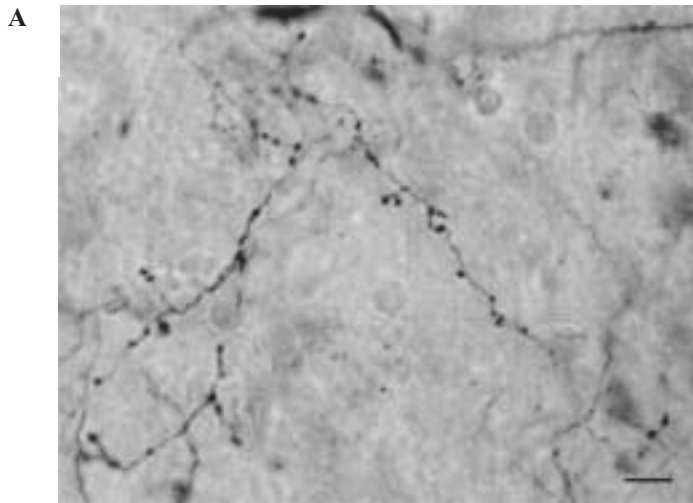
this view best explained the transience and subsequent recovery of motor function following a cortical lesion as well as the widespread pattern of limb movements involved in Jacksonian epilepsy, a form of focal epilepsy originating in the motor cortex (see Murphy and others 1980). Beginning in the 1990s, several studies singly and more persuasively in combination have reinforced the Jackson-Walsh perspective on the function and organization of the motor cortex. This integrated view of motor cortical function forms the conceptual underpinning of this review. I will describe the modern studies that have contributed to the rediscovery of the Jacksonian perspective. These include kinematic, neuroimaging, neuroanatomical, and neurophysiological observations that together begin to build the proof sought by Penfield and Rasmussen (1950).

### Neuroanatomical Observations

Studies involving the superposition of topographical maps of the motor cortex obtained by microstimulation and morphological connectivity maps obtained by tracer injections in physiologically identified sites have shown that motor cortical zones controlling various forelimb segments and those controlling antagonistic muscles are strongly interconnected by intrinsic horizontal collaterals (Huntley and Jones 1991; Keller 1993; Tokuno and Tanji 1993; Capaday and others 1998). These intracortical connections have been suggested to be the anatomical substrate of muscle synergies involved in coordinated multijoint movements (Huntley and Jones 1991). For example, when the neuroanatomical tracer horse radish peroxidase is injected at a point in the motor cortex identified by microstimulation to activate intrinsic thumb

muscles, retrogradely stained neurons are found in wrist, elbow, and shoulder regions. This shows that intrinsic connections exist between the representations of distal hand and more proximal muscles. Within this massive pattern of intrinsic connections, physiologically identified motor cortical points controlling antagonistic muscles are also linked by intracortical collaterals (Capaday and others 1998). This finding implies that there exist motor cortical circuits for the coordination of antagonistic muscles (see also Humphrey and Reed 1983). The spinal cord circuits impose a single coordination pattern between antagonistic muscles, reciprocal inhibition (Sherrington 1913; e.g., see also Lavoie and others 1997; Ethier and others 2003). The cortical connections between motor cortical points controlling antagonistic muscles are likely to provide a greater variety of muscle coordination patterns such as the triphasic electromyographic (EMG) pattern during rapid movements and co-contraction of antagonists.

Huntley and Jones (1991), as well as Keller (1993), interpreted the pattern of connectivity as being point-to-point on the basis of the distribution of stained axon fragments. Thus, in their view, a cortical point controlling, for example, the wrist connects to a cortical point controlling the shoulder but not to points that may be in between such as the elbow points. However, in the process of examining the neuroanatomical material of our study (Capaday and others 1998), we were struck by the fact that most synaptic boutons appeared to be located along the axons (i.e., bouton en passant) rather than at terminal fields (Fig. 2A). Central synapses are morphologically different from the neuromuscular junction where the synaptic boutons are located exclusively at the terminal field of the axon. In the motor cortex, there are a considerable number of en passant boutons (Fig. 2A). It can be seen that terminations are present all along the axon collaterals and appear as small swellings of the axon or as swellings at the tip of fine stalks. Most of these terminals form asymmetric (excitatory) synapses, as determined by electron microscopy (Fig. 2B). There are no evident terminal arborizations (see also Ghosh and Porter 1988) like those of primary visual cortex neurons (Gilbert 1998; Bosking and others 1997). The axonal arbor of cat motor cortex neurons thus resembles that of hippocampal pyramidal neurons (Sik and others 1993). Figure 3 shows a single reconstructed layer V neuron of the motor cortex and its axonal arbor. The neuron was located at a point where microstimulation at threshold intensity activated the elbow flexor muscle, brachialis. It can be seen that the axon collaterals extend horizontally a very long distance (about 3.5 mm in this example) and are studded with boutons all along their course. Moreover, the collaterals course through a variety of points at which muscles acting at other joints are represented (e.g., wrist and shoulder). On this basis, it may be suggested that motor cortical neurons do not make point-to-point connections but rather chain together the representations of a variety of muscles, reminis-



**Fig. 2.** *A*, Example of biocytin-labeled intracortical axons. Note the numerous boutons en passant (club-like swellings) along the axonal branches. Scale bar in (*A*) represents 10  $\mu\text{m}$ . *B*, Biocytin-labeled axon terminal forms asymmetrical synapse (arrow) on a dendritic spine(s); asymmetric synapses are excitatory. Note the postsynaptic membrane thickening and the presence of a mitochondrion in the presynaptic terminal. The arrowhead near the top of the figure depicts another asymmetrical synapse formed by an unlabeled bouton. Scale bar in (*B*) represents 500 nm.

cent of the Jacksonian perspective. Thus, a cortical point controlling a given muscle(s) communicates its activity to a large neighborhood in which a variety of other muscles are represented. In the primary visual cortex (V1), iso-orientation columns in different parts of the visual field are specifically interconnected (Bosking and others 1997). The implication is that different parts of the visual field are integrated in V1 (Gilbert 1998). In a similar way, different parts of the musculature may be functionally integrated by the motor cortical circuitry. Such spatial integration may be a general principle of cortical function.

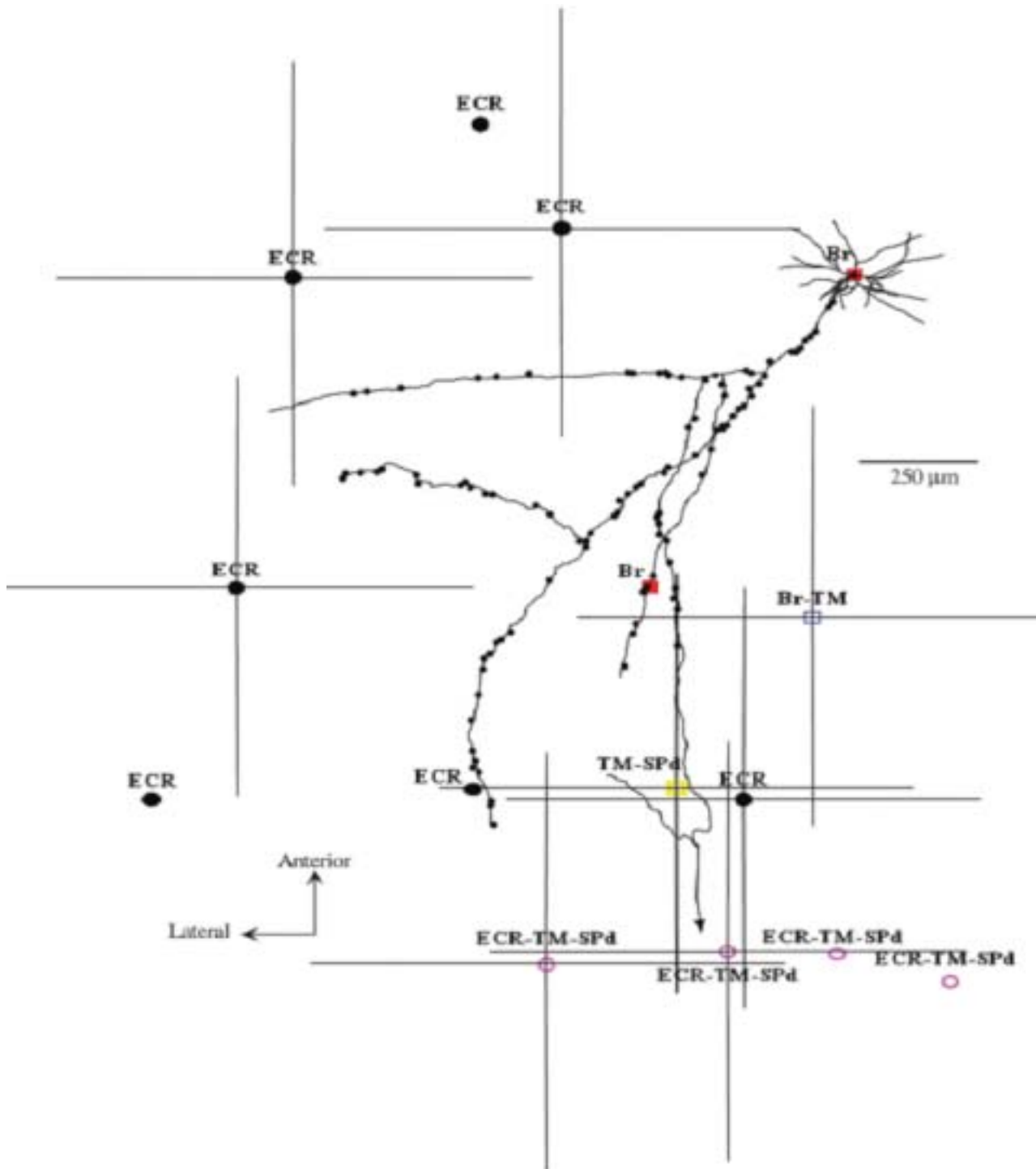
It is important to consider that the intrinsic motor cortical connectivity may have its actions reinforced by the extensive intraspinal branching of individual corticospinal axons (Shinoda and others 1976; Tantisira and others 1996; McKiernan and others 1998). For example, experiments using spike-triggered averaging of EMG

activity revealed that 50% of corticospinal neurons project to both proximal (e.g., shoulder, elbow) and distal motoneuron pools (e.g., wrist and hand); some control muscles at three different forelimb segments (McKiernan and others 1998).

## Neurophysiological Observations

### *Microstimulation Studies*

Further support for the idea of embedded muscle synergies comes from studies by Armstrong and Drew (1985) on the cat motor cortex. They showed that microstimulation, even at threshold, elicits a widespread pattern of muscle activation, as we have also observed (Capaday and others 1998; Schneider and others 2001). Similar results were obtained in the squirrel monkey (Donoghue and others 1992). Our recent experiments in cats have



**Fig. 3.** Camera lucida drawing of a single biocytin-labeled motor cortical layer V pyramidal neuron, reconstructed from horizontal sections (i.e., viewed from above). Microstimulation at that point elicited a response in the elbow flexor brachialis (Br). Note the extensive axonal arbor studded with boutons (dots) all along its course. The boutons have been purposely enlarged to make them readily visible. Note also that several cortical points controlling muscles at different joints (e.g., shoulder muscles such as the teres major [TM] and the spinodeltoid [SPd] and wrist muscles such as the extensor carpi radialis [ECR] may be contacted). The crosses centered at each microstimulation point represent an estimate of size of the dendritic arbor of the local pyramidal neurons.

shown that this is not due to the spread of current from the tip of the microelectrode nor the result of impulse conduction along the lengthy intracortical axonal arbor

(Schneider and others 2001). We microstimulated every 500 μm along mediolateral rows and recorded the evoked EMG responses of up to a dozen forelimb mus-

cles located between the shoulder and digits. A consistent finding in all animals studied was that along a given row, distal muscle responses could be elicited from medially situated cortical loci and, conversely, proximal muscle responses from laterally situated cortical loci, contrary to what is reported in classical maps of the cat motor cortex (e.g., Woolsey and others 1952; Nieoullon and Rispal-Padel 1976). In many such cases, the evoked EMG responses were such that the largest responses from a distal muscle were obtained by stimulation at a medially situated point and those of a proximal muscle from a laterally situated point (Fig. 4). A Spearman rank order analysis showed that there was no correlation between cortical position and where the peak response of a given muscle occurred. These quantitative results strongly support the view that in the forelimb area of the cat motor cortex, there exist widespread colonies of corticospinal neurons with common spinal cord targets, as first suggested by Phillips and colleagues (Andersen and others 1975). The repeated noncontiguous representation of a muscle across the motor cortex is consistent with the Jacksonian perspective (see also Kwan and others 1978). Jackson (1882) had clearly anticipated the multiple noncontiguous representations of muscles when he wrote, "There is no localization of function in the sense that every part of a centre represents an external muscular region in the same way as all other parts of the centre do. . . . Each part of a centre represents the whole of a muscular region, and each part of it represents the whole region differently" (see further details on motor cortical maps in Sanes and Scheiber 2001). These observations do not challenge the well-established fact that the arm, leg, face, and so forth are represented in different parts of the motor cortex. Rather, they demonstrate that within a given area, such as that of the arm, there is no simple spatially segregated somatotopic organization.

In the preceding account of the evidence that muscle synergies are represented in the motor cortex, the reader should not infer that these are hard-wired entities. On the contrary, the two following sections develop the idea that movement-related muscle synergies may be dynamically created by the operations of motor cortical circuitry.

### *Operational Principles and Neural Activity in Motor Cortex*

Kinematic analysis of human pointing movements has shown that elbow and shoulder motions are tightly coupled (Soechting 1984). The neural basis of this observation remains to be elucidated, but clearly motor cortical circuits may be involved. Several observations support this idea. Donoghue and colleagues (1992) concluded from their mappings of the squirrel monkey motor cortex that "patterns of organization that include functional combinations of muscles must be considered." In Rhesus macaques, Park and colleagues (2001) reported the existence of a motor cortical region containing neurons that specify functional synergies of distal and proximal muscles. In humans, Sanes and others (1995) suggested that

the overlap of cortical representation obtained by fMRI may mediate motor functions requiring coordinated neural processing for finger and wrist action, rather than discrete control implied by somatotopic maps. This finding is in keeping with one of Jackson's compelling arguments in support of his integrated view of motor cortical function. Jackson (1931, vol. 1, p 69) wrote,

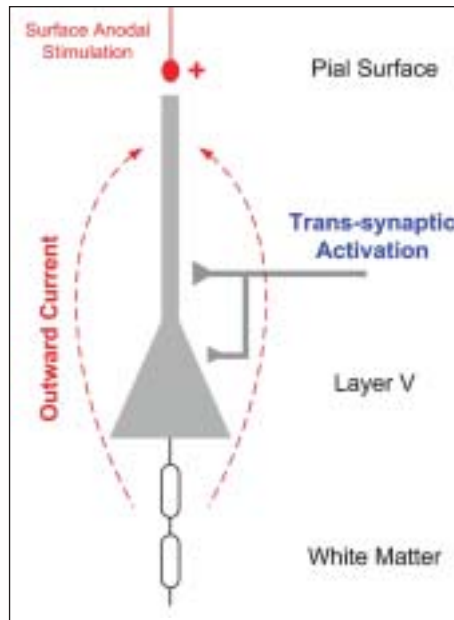
Because the movements of the thumb and fingers could scarcely be developed for any useful purpose without fixation of the wrist (and of parts further and further in automaticity according to the force required), we should a priori be sure that the centre discharged, although it might represent movements in which the thumb had the leading part, must represent also certain other movements of the forearm, upper arm, etc., which serve subordinately.

The recent data obtained by Poliakov and Schieber (1999) further corroborate Jackson's idea. Neural activity of motor cortex neurons was recorded during individual finger movements made by monkeys; wrist muscle activity is inherent to this task. Most neurons were active during many or all of the movements performed. A cluster analysis of motor cortex neural discharges revealed fewer clusters (functional grouping of neurons with similar movement-related properties) than there were movements. They concluded that motor cortex neurons are active during a wide range of finger and wrist movements, rather than being narrowly involved with particular movements (e.g., that of a single finger).

We recently showed that during pointing, a natural human gesture, activation of shoulder, elbow, and wrist muscles involve, at least in part, common motor cortical circuits; that is, they are controlled in an integrated manner (Devanne and others 2002). We used focal transcranial magnetic stimulation (TMS) to measure the input-output (I/O) curves of proximal (anterior deltoid [AD] and triceps brachii) and distal muscles (extensor carpi radialis [ECR] and first dorsal interosseus [IDI]) during isolated contraction of one of these muscles or during selective coactivation with other muscles involved in pointing. The I/O curves are a measure of excitability of the corticospinal pathway as a whole (Devanne and others 1997). Compared to an isolated contraction of the ECR, the plateau-level of the ECR sigmoid I/O curve increased markedly during coactivation with the AD while pointing (Fig. 5A). By contrast, the I/O curve of AD was not influenced by activation of the more distal muscles involved in pointing (Fig. 5A). Moreover, the IDI I/O curve was not influenced by activation of the more proximal muscles. Three arguments argue for a cortical site of facilitation of ECR motor potentials (see Box 1). First, ECR motor potentials evoked by a near-threshold TMS stimulus were facilitated when the AD and ECR were coactivated during pointing but not those in response to a near-threshold anodal electrical stimulus (Fig. 5B). Second, the ECR H-reflex amplitude was not found to be task dependent, indicating that the recruit-

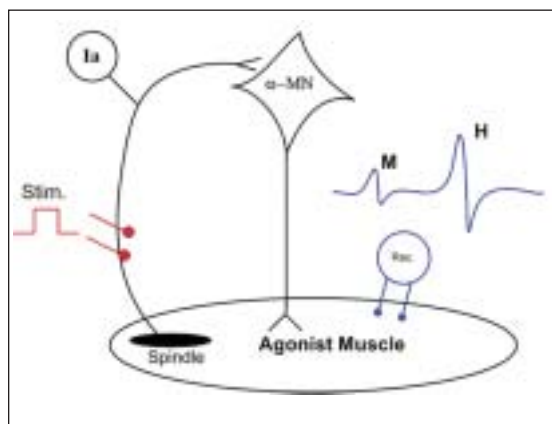
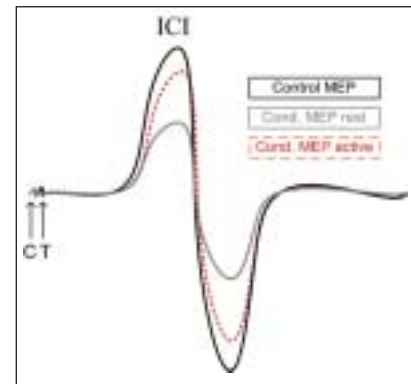


### Box 1: Basis of Neurophysiological Methods Applied to Human Subjects

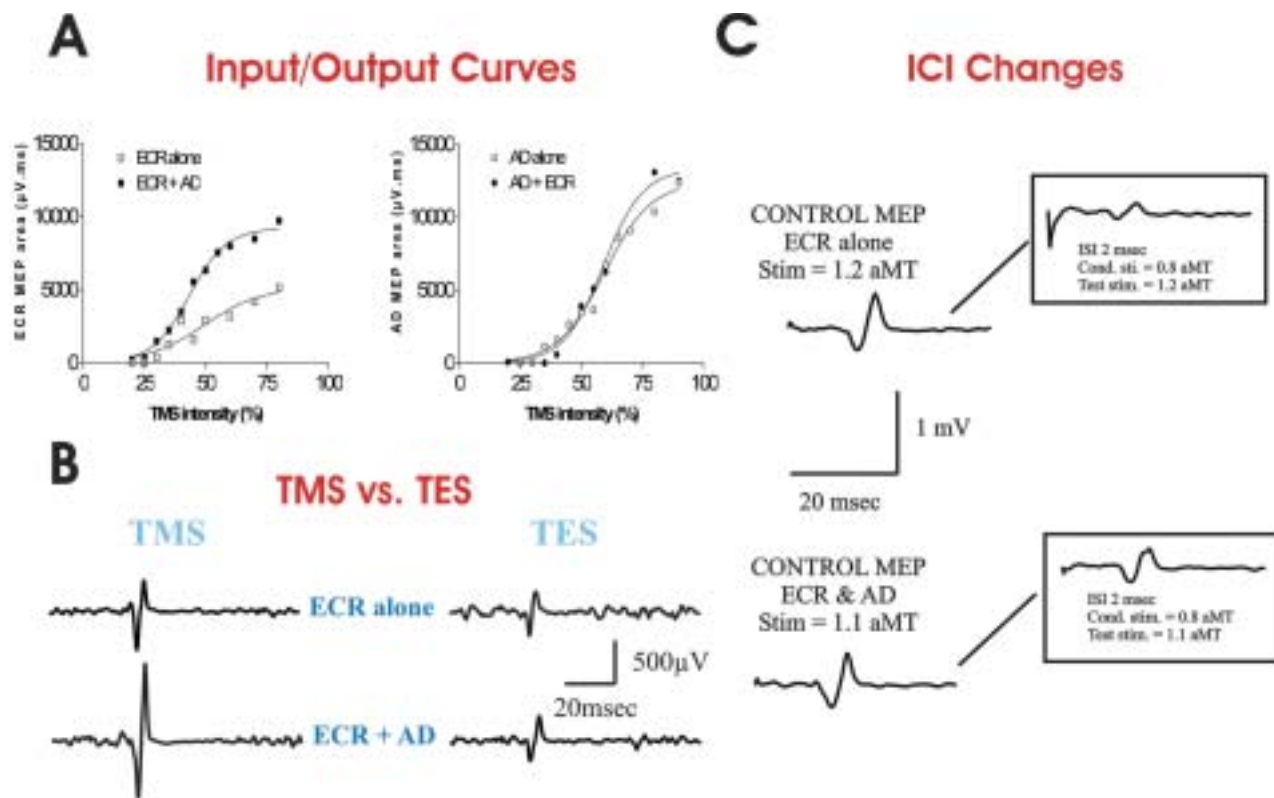


Threshold anodal stimuli (+) applied to the surface of the cortex or the scalp activate corticospinal neurons distal to their soma, at the first or second node of Ranvier (Amassian and others 1987). An anodal electrical stimulus hyperpolarizes the apical dendrites of layer V corticospinal neurons and produces outward current flow (depolarizing) from the deeper parts of the neurons, such as the initial segment or the first nodes of Ranvier. The threshold for action potential initiation is lower in these parts of the neuron than at the soma. Because the site of action potential initiation is relatively distant from the soma, the evoked corticospinal discharge is relatively uninfluenced by the state of intracortical excitability (Rothwell 1997). By contrast, threshold magnetic stimuli activate corticospinal neurons transsynaptically (Rothwell 1997). Consequently, the evoked corticospinal volley is more dependent on the state of intracortical excitability (Rothwell 1997; Devanne and others 2002).

Paired-pulse magnetic stimuli to the motor cortex can be used to measure changes in intracortical inhibition (Kujirai and others 1993). This inhibition has been shown unequivocally to be of intracortical origin (Di Lazzaro and others 1998), and there is pharmacological evidence that it depends on GABAergic neurons (Ziemann and others 1996). The method involves delivering a submotor threshold conditioning stimulus to the motor cortex some 2 to 4 ms prior to a supramotor test stimulus. When the subject is at rest, a sizable reduction of the elicited motor-evoked potential (MEP) is observed. However, when the test muscle is voluntarily contracted, the conditioning stimulus produces markedly less inhibition (i.e., the elicited MEP is larger than at rest). This is the important fact underpinning use of this method to study task-dependent changes of motor cortical involvement. The conclusion is that when the motor cortex is engaged into action, there is not only an increase of excitatory activity but also a measurable reduction of inhibition (Ridding and others 1995).



When measurements between tasks are made at matched levels of electromyographic activity (i.e., the recruitment level of the  $\alpha$ -motoneuron pool), the H-reflex is a measure of the efficacy of synaptic transmission from the Ia-afferent to the  $\alpha$ -motoneurons (Capaday 1997, 2002). The M-wave, resulting from direct stimulation of the axons of the  $\alpha$ -motoneurons, serves as a measure of stimulus strength. The recruitment gain of a motoneuron pool is defined as the rate of recruitment by an input pathway such as the corticospinal tract. It has been suggested that the recruitment gain may differ from one task to another (Kernell and Hultborn 1990). A task-dependent change in the input-output curve of MEPs, unaccompanied by a change in monosynaptic reflex amplitude, implies that it is not due to a change of the recruitment gain of the  $\alpha$ -motoneuron pool (Capaday 1997; Devanne and others 1997).



**Fig. 5.** A, When pointing, the input-output (I/O) curve of the extensor carpi radialis (ECR) is markedly enhanced in comparison to its I/O curve with the arm in the same position but supported proximally such that the anterior deltoid (AD) muscle (arm elevation) is inactive. Note that the ECR muscle is equally activated whether the proximal arm is supported or not. In contrast, when the wrist is supported while pointing and thus the ECR is inactive, the I/O curve of the AD is the same as when the wrist is not supported and the ECR thus active. B, Motor-evoked potentials (MEPs) evoked by near-threshold transcranial magnetic stimulation (TMS) or by near-threshold transcranial electric stimuli (TES). Each trace is the average of eight individual responses. Note how the ECR MEPs elicited by near-threshold TMS ( $1.1 \times$  active motor threshold [AMT]) are enhanced when the ECR and AD are coactive. By contrast, ECR MEPs elicited by near-threshold TES ( $1.1 \times$  AMT) are not enhanced when the ECR and AD are coactive. C, Example showing that coactivation of AD and ECR led to a decrease of intracortical inhibition (ICI) compared to when the ECR was activated alone. Compare the size of the MEP at an interstimulus interval of 2 ms at the top of the panel versus the one at the bottom of the panel.

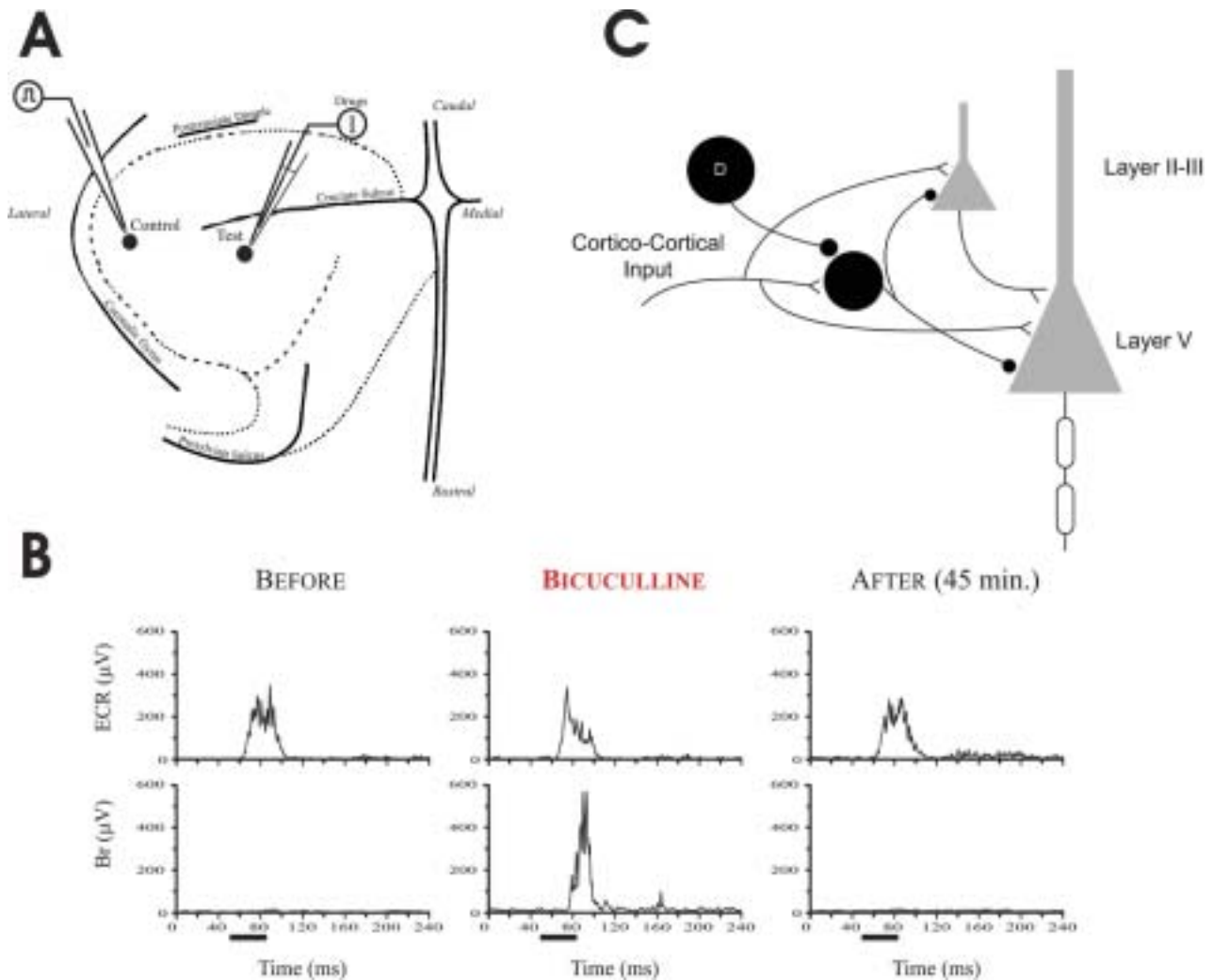
ment gain of the ECR a-motoneurons pool did not differ between tasks (Kernell and Hultborn 1990; Devanne and others 1997). Finally, in comparison with an isolated ECR contraction, intracortical inhibition (ICI) tested at the ECR scalp site was decreased during pointing (Fig. 5C). These results suggest that activation of shoulder, elbow, and wrist muscles involved in pointing appear to involve, at least in part, common motor cortical circuits. By contrast, in the pointing task, the motor cortical circuits involved in activation of the intrinsic finger muscle, 1DI, appear to act independently. In pointing, there is essentially no dynamic mechanical interaction between the index finger and the wrist. However, it may turn out that in other tasks, such as manipulating an object, evidence for common motor cortical control of hand and wrist muscles may be found.

The neurobehavioral results of Devanne and others (2002) demonstrate that the motor cortex controls task-related muscles as a whole, an idea that is also consistent with single-unit recording experiments in the monkey

(Holdefer and Miller 2002). They showed that in pointing movements made by monkeys to different targets, a large proportion of motor cortex neurons were clustered into groups related to distinct muscle synergies having a functional role, such as extending the limb. Taken together, these observations suggest that functional coupling of motor cortical circuits is a dynamic and task-dependent process.

A particularly striking finding was the demonstration by Graziano and colleagues (2002) that by prolonging the duration of microstimulation to some 300 to 500 ms, roughly equal to the duration of natural movements, coordinated and seemingly goal-directed movements can be elicited in the macaque. This is very strong evidence in support of Jackson's hypothesis, as a wide variety of movements were elicited from different parts of the motor cortex. It is not known, however, whether a cortical point contains all the circuitry needed to elicit a movement or whether in fact it acts by recruiting functionally linked neighboring points. The anatomical





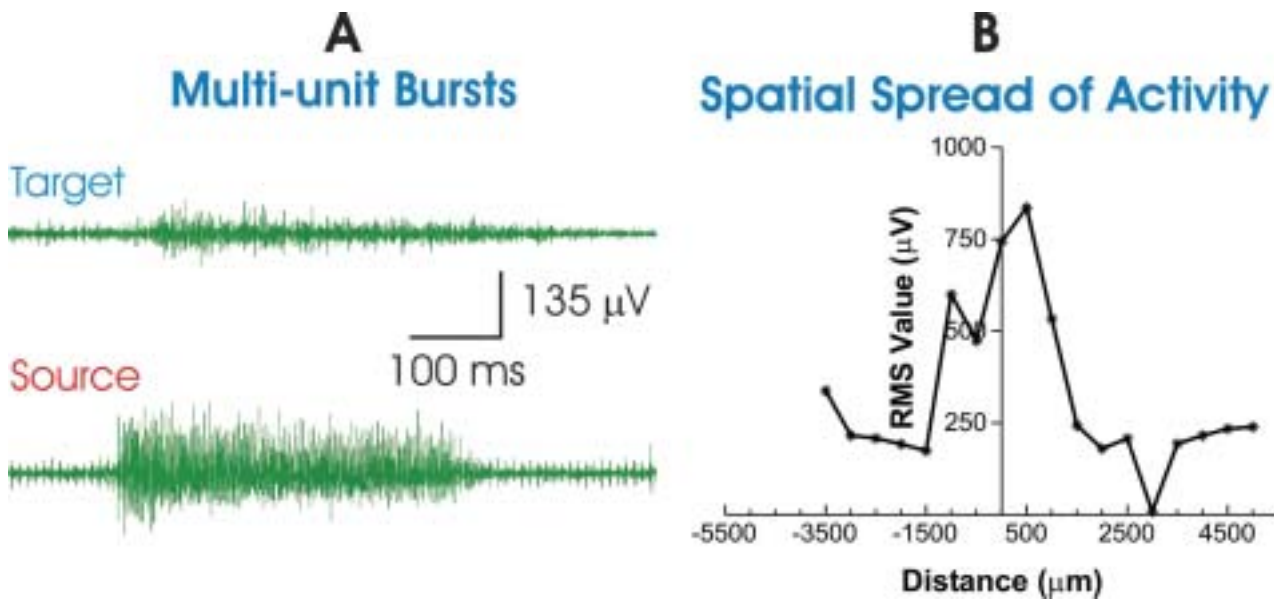
**Fig. 6.** *A*, Schematic illustration of the basic experimental arrangement in the right motor cortex of the cat as described in the text. The distance between control and test points in this illustration is not necessarily to scale. *B*, Effects of bicuculline ejection in a brachialis test cortical point. The stimulus current to the control extensor carpi radialis (ECR) point was  $10 \mu\text{A}$  ( $1.2 \times$  threshold) and was delivered starting at 50 ms. The dark bar under the time axes indicates the onset and duration of the stimulus train. The recording shown of the combined ECR-brachialis response was obtained 2 min after beginning of the bicuculline ejection. The effect produced by bicuculline was terminated some 45 min after stopping the iontophoretic current. The distance between the control and test points was  $2400 \mu\text{m}$ . Each electromyographic record is the average of eight consecutive responses. *C*, Neural circuit suggested to explain how local disinhibition at a motor cortical point allows it to be functionally linked with another motor cortical point. Inhibitory interneurons are shown in black and pyramidal cells in gray. The inhibitory interneuron labeled *D* is hypothesized to inhibit the local inhibitory neuron on which cortico-cortical afferents impinge. The cortical layers refer to the positions of pyramidal neurons, not those of the inhibitory neurons or to the positions of synapses.

organization described in the preceding section and the Jackson-Walsh hypothesis suggests the latter (see Fig. 1 in Walsh 1943). The neural processes that may be involved in the functional linking of motor cortical points are discussed next.

### Operation of the Motor Cortical Circuitry

Although much is known on the anatomical organization of the motor cortex and the relation between the firing of motor cortex neurons and movement parameters (Jasper and others 1958; Evarts 1968; Kalaska and Crammond 1992; Georgopoulos 1999; Scott and others 2001; Kakei

and others 2003), little is known on the nature of its circuitry or its operation. In the study by Schneider and colleagues (2002), we sought to understand the basic neural processes involved in the functional linking of motor cortical points. We asked which of the two basic neural mechanisms, excitation or inhibition, is required to functionally link motor cortical points. In the ketamine-anesthetized cat, a microstimulation electrode was positioned at a point (control point) that was identified by the following three characteristics of the EMG responses: 1) the muscle(s) activated at threshold; 2) additional muscles recruited by suprathreshold stimulation, if any; and 3) the EMG response latencies. A second distinct point



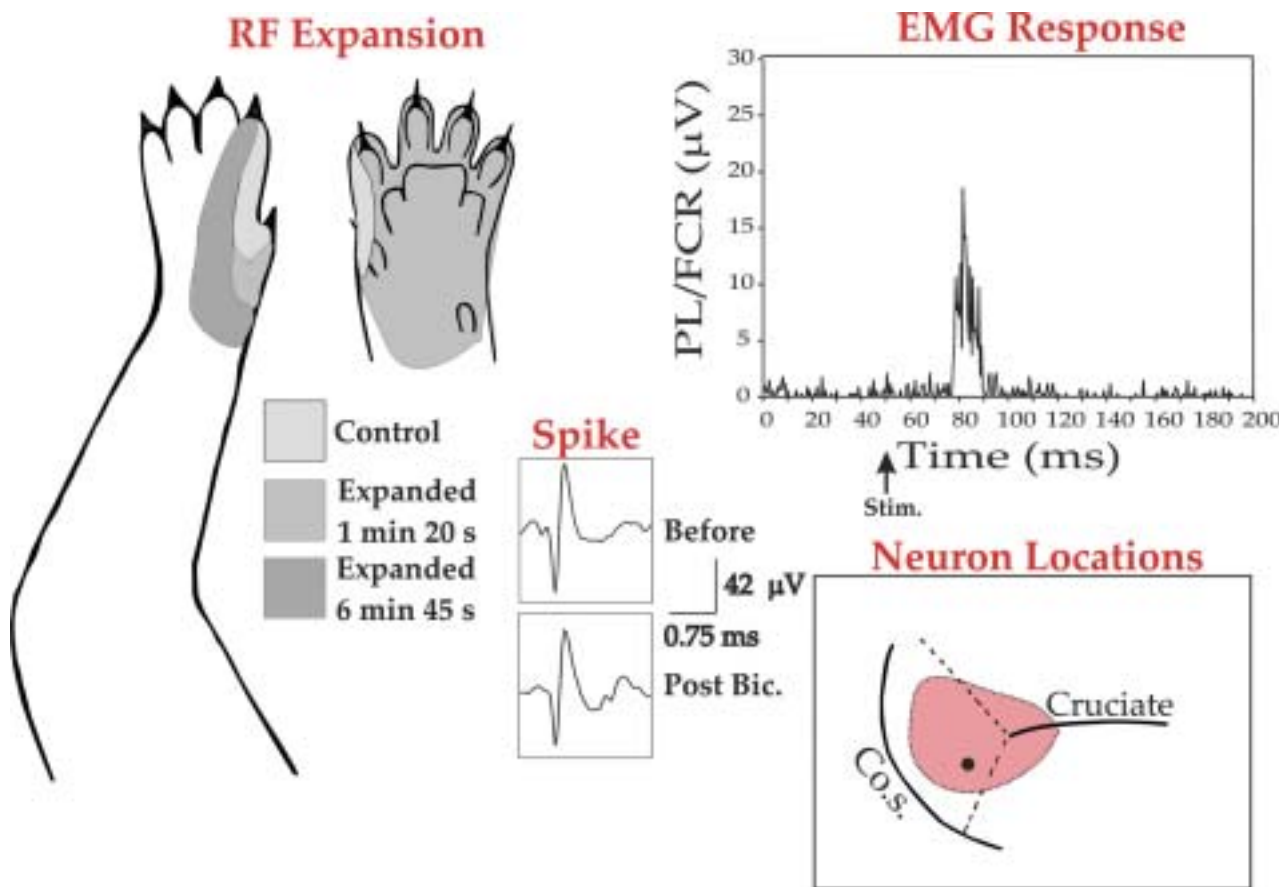
**Fig. 7.** Focal bursting at a motor cortical point (source) was induced by iontophoretic release of bicuculline. Some 2 to 5 min after the start of ejection, focal quasi-periodic bursts (circa 0.75 Hz at onset) are generated spontaneously. *A*, Example of spontaneous multi-unit bursts. Note the spread of activity from the source of activity to another point (target) located 2500  $\mu$ m more laterally. Note the propagation delay from source to target. *B*, The root mean square value (RMS) of the multiunit bursts was measured along a row every 500  $\mu$ m and plotted against the distance from the source of activity (nominally located at the zero coordinate on the abscissa). The recording electrode was always driven to a depth of 1400  $\mu$ m below the cortical surface. The important point illustrated in (*B*) is that activity can spread a considerable distance across the motor cortex.

(test point) producing activation of a muscle at a different joint was then identified. At this test point, the GABA<sub>A</sub> receptor antagonist bicuculline (disinhibition) was ejected iontophoretically while stimulating the control point just above threshold intensity (Fig. 6A). This resulted in a combined response consisting of the response normally elicited at the control point plus that elicited at the test point (Fig. 6B). Thus, an artificial muscle synergy was produced following disinhibition of the test point. This was never the case when glutamate was ejected at the test point, even when suprathreshold stimuli were used. Therefore, simply increasing the excitability of a cortical point was not sufficient to release the muscle(s) represented at that point into a muscle synergy. When kynurenate, a broadly acting excitatory amino acid receptor antagonist, was ejected at the test point following its disinhibition by bicuculline, stimulation at the control point no longer elicited a combined response. This shows that the functional linking of the two cortical points was mediated synaptically and was not due to spread of the stimulating current. Thus, release from inhibition may be one of the neural mechanisms involved in functionally linking motor cortical points. This functional linking may be part of the ensemble of motor cortical mechanisms involved in the recruitment of muscle synergies subserving movements.

The neural circuit shown in Figure 6C was suggested to explain these observations. It is clear that under normal circumstances, the activity transmitted from the microstimulated point to the test point is ineffective in evoking a response from that point. We suggested that

this is because the input is normally blocked in at least two ways. One site at which the input may be inhibited is at the soma of the corticospinal neurons in layer V (output neurons). This may be because of ongoing GABAergic activity, as has been suggested to occur in the brain (e.g., Otis and Mody 1992). Another possibility is that the afferent volley from the control point activates inhibitory interneurons at the test point that in turn synapse onto the local corticospinal neurons (Fig. 6C). The circuit presented in Figure 6C implies that functional linking occurs when the local inhibitory neurons are themselves inhibited. The question that thus arises is how during natural activity are the local inhibitory cells disinhibited? In the hippocampus, so-called "master" inhibitory neurons, which are specialized to innervate other GABAergic interneurons, have been identified (Sik and others 1995; Acsady and others 1996). In the visual cortex, intrinsic connections between GABAergic neurons have also been identified (e.g., Tamas and others 1998). It seems likely, therefore, that in the motor cortex, intrinsic circuits for inhibiting GABAergic interneurons exist. The functional linking of cortical points under natural conditions would therefore involve not only excitation of selected points but also disinhibition of the local inhibitory interneurons. It remains to be determined whether this motor cortical disinhibition process is controlled by thalamic or premotor cortical inputs.

The massive intrinsic connections between cortical points discussed previously may in fact require the sort of physiological stabilizing mechanism just discussed.

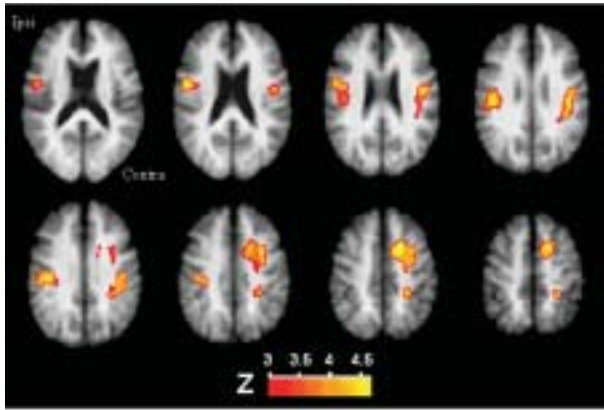


**Fig. 8.** Example of the progressive receptive field (RF) expansion, up to 6 min and 45 sec, of a motor cortical neuron following iontophoretic ejection of bicuculline. The location of the neuron (●) relative to the surface of the cat motor cortex (area 4 g), bounded laterally by the coronal sulcus (Co.s.), is shown in the inset in the lower portion of the figure. The area labeled in pink shows the region in which the other neurons studied were located. The dashed lines delineate the coronal gyrus. Threshold microstimulation (40 mA) at the point where the neuron's spike activity was recorded elicited an electromyographic response in the wrist flexors PL/FCR. The onset of the stimulus train is indicated in the figure. The neuron's spike waveform is shown before and 8 min after the onset of iontophoresis.

Otherwise, activity at a given cortical point would spread well beyond it and recruit muscles that are inappropriate for the intended movement. Such a spread of activity is demonstrable following induction of local bursting activity at a motor cortical point produced by disinhibition with bicuculline. Some 5 min after the start of ejection, focal quasi-periodic bursts (circa 0.8 Hz at onset) are generated spontaneously (Fig. 7A). These local multiunit bursts spread over several millimeters, as shown in Figure 7B. In that example, activity spread 3500  $\mu\text{m}$  laterally from the point of ejection and 5000  $\mu\text{m}$  medially, covering nearly the whole mediolateral extent of forelimb representation of the cat motor cortex.

Most neurons in the motor cortex receive sensory inputs that contribute to the control of motor outputs (e.g., Welt and others 1967; Asanuma and Rosen 1972; Lemon and Porter 1976). What happens to the sensory inputs to motor cortical neurons in the event that local inhibition is reduced? We have recently investigated this issue in the cat motor cortex (Capaday and Rasmusson 2003). The receptive field of single neurons was first

mapped and reexamined after iontophoretic ejection of bicuculline. In all 21 neurons examined, bicuculline produced on average a fourfold expansion of the receptive field (RF) size, an example of which is shown in Figure 8. Expansion was seen most often in the proximal-distal axis but was also commonly seen in the mediolateral axis. The expansion was usually restricted to the dorsal or ventral surface of the paw on which the original RF was located. However, in three neurons in which the pre-drug RF was on the dorsal surface of the paw, the expansion included part or the entire ventral surface. No change in the modality or RF stimulus threshold was observed following bicuculline. We concluded that if local disinhibition is involved in the functional linking of motor cortical points for output commands, this may be also accompanied by expansion of the receptive fields. This may be of functional value because motor cortical output neurons would receive sensory input integrated over a larger area of the limb. The role of local inhibitory control of sensory inputs to motor cortex neurons may thus be different than that in the sensory cortex where it



**Fig. 9.** Transverse sections through a mean magnetic resonance (MR) image, created from a voxel-by-voxel mean of the volumetrically normalized MR images of eight of the normal control subjects. Superimposed are the regions of significantly increased flumazenil binding found in the amputees. Three regions are seen: symmetrical increases in flumazenil binding in the sensorimotor cortices bilaterally and a region of increased flumazenil binding encompassing the supplementary motor area and the lateral premotor area of the hemisphere contralateral to the amputation. The terms *ipsi* and *contra* refer to the hemisphere ipsilateral or contralateral to the amputation, respectively. The Z-score color bar graph indicates the level of statistical significance in units of standard deviation.

is thought to restrict RF size (Hicks and Dykes 1983; Alloway and Burton 1991; Tremere and others 2001b; Chowdhury and Rasmusson 2002).

### Implications for Neurorehabilitation

That task-related muscles are controlled as a whole by the motor cortex provides some insight into the neurological deficits following a stroke. These deficits are not simply weakness or paralysis but also improper coordination between limb segments (e.g., Beer and others 1999; Cirstea and others 2003; Li and others 2003). At the structural level, this may be explained by a disruption of the connections between cortical points and thus a disjunction of the representation of functional muscle synergies. A prominent feature of movements made by stroke patients is the irradiation of muscle activity beyond what is needed. For example, in stroke subjects, there is a greater enslaving (forced coupling) of finger movements; that is, finger movements are less individuated than in normal subjects (Li and others 2003). Given the fragility of some types of inhibitory interneurons to cortical insults such as hypoxia (Sloper and others 1980; Ribak 1991), it may be speculated that this lack of coordination may be partly due to improper functioning of the motor cortical inhibitory network. Although there is as yet no direct evidence in support of this idea, there are many reports of changes in GABA levels and GABA<sub>A</sub> receptor numbers in the cortex following damage to afferent inputs (Hendry and Jones 1986; Micheva and Beaulieu 1997; Tremere and others 2001a) and in the sensorimotor cortex of amputees (Capaday and others 2000). In the latter study on human amputees and nor-

mal subjects, volumes of distribution (Vd) of GABA<sub>A</sub> receptors were determined from <sup>11</sup>C-flumazenil binding measured with positron emission tomography. The Vd is directly proportional to the number of available receptors (Bmax), providing that there are no pathological changes of receptor affinity (Richardson and others 1996; Koeppe and others 1998). <sup>11</sup>C-flumazenil is a central benzodiazepine antagonist and serves as a GABA<sub>A</sub> receptor marker (Richardson and others 1996; Koeppe and others 1998). The strength of inhibition in the motor cortex was measured with paired-pulse transcranial magnetic stimulation. In 6 amputees taken as a whole and compared with 24 normal subjects, there was a highly significant increase in <sup>11</sup>C-flumazenil binding in the upper-limb region of primary sensorimotor cortex bilaterally and in the medial frontal cortex of the hemisphere contralateral to the amputation (Fig. 9). Surprisingly, however, using paired-pulse magnetic stimulation to measure the time course and strength of motor cortical inhibition, no differences were found between the amputees and matched control subjects.

We suggested that the increased <sup>11</sup>C-flumazenil binding may reflect upregulation of GABA<sub>A</sub> receptors to compensate for a decrease in the GABA content or activity of GABAergic neurons. Upregulation of GABA<sub>A</sub> receptors may also indicate that long-term changes require stabilization of cortical reorganization. For example, in adult monkeys, large-scale sprouting of long-range intracortical connections is evident in S1 several years after forelimb trauma (Florence and others 1998). Such sprouting may upset the balance between intracortical excitation and inhibition. It is possible, therefore, that the increased number of GABA<sub>A</sub> receptors we reported is a natural counterpart of this increased collateral sprouting. This also suggests an explanation for why ICI was no different in the amputees compared with the normal subjects; inhibition remains balanced with excitation. The important point is that changes in GABAergic neurochemistry are associated with neurological damage. How this may affect the functioning of a cerebral area, such as the motor cortex, remains to be explored.

In any case, the integrated nature of motor cortical control strongly suggests that neurorehabilitation programs should be aimed at reinforcing complete tasks, such as reaching to grasp or standing up from sitting. Indeed, the idea of dealing with complete movement synergies has been an important concept in rehabilitation programs. Our current understanding of motor cortical function set out here substantiates this approach and will hopefully contribute to its further progress.

### Conclusion

In developing this thesis, I have focused implicitly in the words of Jackson on the “leading part,” but what is overtly observable of a movement is like the tip of an iceberg: There is much hidden from the naked eye. The postural adjustments associated with voluntary movements illustrate this beautifully. For example, increased

motor activity in leg and back muscles automatically and unconsciously precedes the raising of one's arm while standing (Dick and others 1986). The combined action of these muscles ensures maintenance of upright posture despite the forward shift of the body's center of gravity produced by raising the arm. Anticipatory postural adjustments associated with voluntary movements are a classic example of feedforward control—counteracting a disturbance in advance of its actualization. In an important series of experiments, Massion and colleagues showed that stimulation of the motor cortex in the cat produced a contralateral forelimb flexion and nearly simultaneous ipsilateral postural responses (reviewed in Massion 1992). It was suggested that the motor command to the forelimb was dispatched to the spinal cord as well as to the brainstem motor centers, which in turn commanded the necessary postural adjustments to the other limbs (Gahéry and Nieoullon 1978). This is a nice example that illustrates the principle and supports the postulate of integrated motor cortical control on a wide scale.

In summary, motor activity is inherently an integrated life function, and this is strikingly reflected in the integrative nature of motor cortical structure and function.

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