CHAPTER 4

NEURONAL SUBSTRATE FOR VOLITIONAL MOVEMENT

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SUMMARY

The act of reaching toward and grasping an object is perhaps one of the best examples of volitional movement. Although the control of this movement is poorly understood, the motor cortex has been considered essential in this regard. While neuroanatomical studies suggest which structures may be involved in producing volitional movement, they cannot describe their functional organization. Only recently have neuronal studies been combined with behavioral paradigms to examine the control of this movement. I will review some historical studies of volitional movement and compare these to recent neurophysiological studies of more natural movements which have shown that characteristics of volitional action may be encoded throughout a large portion of the CNS and not restricted to discrete structures.

INTRODUCTION

In our attempt to understand the process subserving volitional limb movement, we must confront a major impediment to this study. The substrate responsible for generating these movements is covert - concealed within the CNS. Unlike sensory stimuli, which can be identified and detailed externally before the corresponding central response is investigated, the fundamental properties of movement control are far from obvious. This is especially true when considering movements rich in behavioral expression, such as reaching and grasping.

Historically this problem has been approached in a functional-anatomical way through localization. Critical to this approach is the assumption that specific qualities of movement reside in specific structures within the CNS. The motor cortex, for instance, has been considered to be the primary region of the cerebrum responsible for the control of voluntary movement; thus lesions of motor cortex should lead to paralysis. The difficulty with this approach becomes apparent if the assumed quality is not localized. Many cortical and subcortical structures, in fact, participate simultaneously in the control of volitional movement. Indeed, motor cortical lesions result only in temporary paresis, with the ability to make most voluntary movements returning rapidly. The structures remaining after the lesion are similar enough in operation to the motor cortex that they can compensate for its loss.

I will review selectively the history of localization and motor cortical physiology in an attempt to illustrate how we have arrived at our present level of investigation which emphasizes the role of motor cortex in the behavioral aspects of movement. As this chapter concentrates primarily on the neuronal processing taking place in the motor cortex related to reaching, historically important lesion and anatomical studies will not be discussed in detail. Grasping studies, because of the difficulty in measuring the movement are relatively recent and there have been very few physiological experiments examining reaching *and* grasping. The foundation of motor cortical physiology lies in the concept that explicit regulation of volitional movement resides in this region of the cerebrum. It is likely that the principles of motor cortical physiology derived from the reaching and drawing studies will also be relevant to the control of reaching and grasping.

Initially, physiological studies based on the concepts of localization established the motor cortex as a kind of switchboard, mapping cortical activity to specific muscle activation with a discrete one-to-one correspondence. In contrast to the historical localization techniques, recent physiological and psychophysical findings derived from experiments in which animals actually perform complex volitional movement suggest that the cerebral control of these movements is distributed and that movement parameters are encoded coarsely in the activity of single cells. These studies emphasize the idea that information is continuously transformed during the production of volitional tasks. Distributed systems are characterized by parallel processing and multiple representation of information. For instance, neuronal activity encoding a movement parameter may be found in many different parts of the central nervous system (CNS) simultaneously. Within a given anatomical region of the brain, different parameters may be represented at the same instant. Our evolving studies show that simultaneous

neuronal activity in a distributed system such as the CNS should be considered as a whole when trying to understand the substrate for volitional acts such as reaching and grasping.

HISTORY OF LOCALIZING MOTOR FUNCTION

Only within the last 130 years has the cerebral cortex been considered to have any motor function. Through most of recorded history the cortex was thought to be the dominion of consciousness, a *sensorium commune* without localized function. Motor control was relegated to phylogenetically older parts of the neuraxis. Although the cerebrum was not assigned a large role in motor control, as reviewed by Walker [1], cerebral localization was described at the time of Hippocrates when it was noted that unilateral brain injury resulted in movement loss on the opposite side of the body.

Both stimulation and lesion methods have been used to localize function in the CNS. Lesion studies and clinical pathology have provided insight toward some essential roles for the motor cortex. However, because of space constraints I will concentrate only on a review of the stimulation literature.

Although pinching and pricking were used to stimulate the cortex previously, Aldini [2], in the early 1800s, was the first to electrically stimulate the cerebrum. Using the technique developed by his uncle Galvani who experimented with skeletal muscle, Aldini studied the effect of galvanic stimulation on a wide range of decapitated animals. His enthusiasm extended to human subjects. In one report he applied his electrodes across the exposed cortex and right ear of a freshly beheaded man and observed contraction of the right side of the face.

Fritsch and Hitzig [3] in the 1860s applied more localized galvanic stimulation to the cerebrum in rabbits and were able to elicit movement. Later, using bipolar stimulation in a more detailed study in dogs, they found that activation of the frontal cortex produced contraction in the contralateral limbs. They identified the motor cortex as a localized region most responsive to stimulation. Upon removal of this region, they noted a contralateral paresis of the forelimb. More refined studies at the end of the century carried out in the light of the stimulation studies and confined to motor areas of the cortex showed that monkeys [4] could use their contralateral limbs if prompted. Nevertheless these experiments directly supported the idea that motor centers were localized in the cerebral cortex.

Ferrier extended these experiments using faradic stimulation. Whereas galvanic stimulation activated the cortex only once per application, faradic stimulation activated neurons repetitively. This made it possible to use less current to elicit movement and allowed the cortex to be mapped at a higher

resolution. Using frequencies of 30 to 40 Hz, Ferrier observed discrete muscles contracting and was able to map the monkey cortex [5] in detail. These early motor maps spanned both the pre- and postcentral cortices. Horsley and Schaeffer [4] also found the pre- and postcentral cortices to be excitable. However Grunbaum and Sherrington [6] using monopolar stimulation later found that only the precentral cortex elicited movement when stimulated.

These stimulation studies resulted in a map suggesting that the motor cortex was somatotopically organized. Neurons projecting to a portion of the body tended to be located within the same region of the cortex. Adjacent body segments were juxtaposed on the cortical surface. Woolsey [7] later found this pattern to be detailed enough to form a distorted figurine or "simiuculus" on both the pre- and postcentral cortical surfaces. The muscles of the lower face and distal extremities were represented by a disproportionately large cortical area.

About the turn of the century, Jackson was publishing his observations made on epileptic patients with cerebral pathology [8], which were used to support the concept of cerebral localization. As these patients began to seize, he noted that the toe muscles would contract, followed by contractions sequentially up the leg to the trunk and shoulder and finally to the hand. This "march of spasms," he theorized, resulted from the spread of seizure activity across the cortex affecting adjacent regions sequentially. Jackson posited that a relatively direct pathway existed from cortex to the motoneurons and that cortical regions were organized in terms of basic movements that involved widespread activation of multiple muscles (an issue that remained controversial for many years).

At the end of the 19th century the precentral gyrus was considered to be a localized site of motor function. Although there was some controversy whether lesions of discrete areas prevented sensory input from *releasing* motor acts or whether the ablations removed motor capability directly, the cerebrum was considered essential for movement. These ideas were prevalent despite the demonstrations that decorticate animals were capable of moderately complex behavior.

Sherrington's school dominated motor physiology at the beginning of the 20th century. Lesions placed at different levels of the neuraxis led Sherrington to view motor behavior, in general, as an elaboration of simpler reflexes. Leyton and Sherrington [9] mapped the ape cortex with faradic stimulation and defined a set of subareas corresponding to five body portions (face, arm, leg, trunk and head). Using graded stimuli, they were able to elicit fractional movements that could be integrated with other primary fragments to produce seemingly purposeful movement. They viewed the

cortex as a structure that could assemble and integrate combinations of muscular action fragments into different movements.

At the same time other investigators began to measure the effect of cortical stimulation using electromyographic (EMG) recordings. Cooper and Denny-Brown [10] found that cortical stimulation had a "direct" effect on the EMG and that this was evident when stimulating in the frequency range of 4 to 180 Hz. Chang et al. [11] recorded from several muscles simultaneously and found that cortical loci activated by near-threshold cortical stimulation projected to single muscles but overlapped other projection sites. This overlap was more pronounced with higher intensity stimulation. Bernhard et al. [12] recorded descending volleys in the lateral cortical spinal tract (CST) and in dissected ventral roots elicited from 25 Hz cortical stimulation. Since there was only a seven millisecond latency between the first component of the CST volley and activity in the ventral root, the CST was thought to activate α motoneurons monosynaptically. Preston and Whitlock [13] followed by Landgren et al. [14] used intracellular recording to elaborate this finding. They found that excitatory postsynaptic potentials (EPSP) were elicited in α motor neurons at monosynaptic latencies with single shocks applied to the surface of the motor cortex.

These experiments suggested that patches of cortex projecting to particular motoneuronal pools were not discrete but were large (5 to 20 mm^2) [14] and coextensive with cortical areas projecting to different pools of motor neurons. The results of these surface stimulation studies did not support the idea that discrete patches of motor cortex projected to individual forelimb muscles. However, it could be argued that these findings were compromised by current spread through the cortex since relatively strong (2 to 5 mA) stimuli were used in these studies.

In 1968, Stoney et al. [15] reported the results of a study using ICMS (intracortical microstimulation), a technique which was originally developed by Landau et al. [16]. A microelectrode was inserted into layer V or VI of the motor cortex. Motor neurons could be excited with about 1% of the current used for surface stimulation. Using repetitive stimuli (300 Hz) individual muscle contraction was observed and the volume of cortex from which these contractions could be elicited was small and discrete [17]. Using the idea of the cortical column described for sensory cortex, Asanuma and Rosen [17] described the composition of motor cortex in terms of efferent zones.

The idea of a columnar organization as a basis of motor cortical anatomy was developed by Collonier [18]. Two classes of cells were found in the primary motor cortex, stellate and pyramidal cells. The stellate cells with

round cell bodies and non-oriented dendrites were considered interneurons because their axons did not enter the white matter. These were further divided into two types. The double bouquet cells have two major dendritic branches oriented upward and downward, spreading extensively in the vertical plane. These cells are found throughout the thickness of the cortex except in layer I. Their axons entwine the apical dendrites of pyramidal cells and were thought to be excitatory. The other type of stellate cell, termed the basket cell, is found in layers III and V [19]. Its dendrites are star-like and their axons extend horizontally, ending in basket endings (presumed to be inhibitory) on pyramidal cell bodies. Pyramidal cells are found predominantly in layers III and V with the largest cells in the deeper layer. These cells have triangular cell bodies and large apical dendrites that ramify extensively (several mm) in layer I. Their axons may form recurrent collaterals that spread 0.5 to 1 mm horizontally that may also ascend vertically. An important property of pyramidal cells is that their axon collaterals may project horizontally many millimeters, for instance, from area 3b to 4 [20]. A given collateral may generate several terminal patches, oriented radially from layers II to IV, separated by runs of 800μ with no terminals. Thus, an axon originating in 3b may terminate in area 3a as well as in area 4. Since thalamocortical afferents from a given nucleus are thought to terminate within a discrete cortical area, these corticocortical axons may be the most important means of distributing information to different cortical areas. Pyramidal cells also provide the corticofugal output from the motor cortex projecting to most of the subcortical nuclei and to the spinal cord. The distinctive Betz cells of the primary motor cortex are pyramidal cells located in layer V and are among the largest cells in the brain with diameters on the order of 100μ.

More recent studies [21, 22] classified cerebral neurons as either pyramidal or non-pyramidal. The non-pyramidal cells are thought to be intrinsic interneurons possessing spiny and non-spiny dendrites. The non-spiny cells are thought to contain gamma-amino butyric acid (GABA) producing inhibitory postsynaptic potentials (IPSP) in pyramidal cells while the pyramidal cells and spiny interneurons contain the excitatory transmitter glutamate. These anatomical studies suggest that the inhibitory axons are arranged in restricted vertical zones through the cortex and that the basket cell axons, for instance, form an inhibitory surround around a core of excitation produced by the output of the spiny cell axons and recurrent collaterals of the pyramidal cells which would receive input from thalamic afferents. This arrangement would then result in a columnar organization.

Although the horizontal extent of the axon fields of the spiny interneurons were thought to be only 50μ and the *columns* in visual cortex were thought

to be 300-500μ wide, the efferent zones were thought to be one millimeter wide. Input arriving in the upper layers of cortex was thought to be integrated and eventually output via one or a few pyramidal tract cells in layer 5. According to Asanuma and Rosen [17], this output projecting via the CST to motoneuronal pools would activate muscles individually. However the ICMS results showed that agonist finger muscles usually contracted together as did the antagonist muscles about the wrist. Although these cortical efferent zones overlapped those to other muscles, the boundaries between zones were considered sharp. The sharpness was believed to be the result of the low currents used for ICMS in contrast to the less distinct boundaries resulting from the higher current surface stimulation studies.

Columnar organization within the cerebral cortex has been a fundamental concept since the work of Mountcastle [23] showed that cells in cat primary sensory cortex along a radial tangent tended to respond to the same modality of sensory stimuli applied to the same part of the body. Thus, the idea of cortical efferent zones and their similarity to columns described in the sensory and visual cortex was attractive. The entire cerebral cortex was thought to be constructed of basic modules or columns [24]. The differences in the operation of the different cortical areas was attributed to the different afferent projections that each area received. The processing within each column was restricted to the vertical dimension taking place within a restricted volume of cortex.

At that time, in the early 1970s, the controversy over whether movements or muscles were represented in the motor cortex resurfaced. Both rationales were based on the idea that topographical areas of motor cortex would be active sequentially throughout a movement. For instance, during a reach, cells in the shoulder, elbow, wrist and finger areas would change their activity patterns as the corresponding body parts moved. Based on previous studies showing that the motor cortex was somatotopically organized, it was thought that cells in a particular somatotopic division were all active simultaneously. I will refer to this as the *chunk* rationale. If the cortex was organized so that projection areas were large and overlapping, then activation of a given *chunk* would always activate multiple muscles. However if the motor cortex was organized in discrete efferent zones, then muscles would be separately activated from each *chunk*. Though Asanuma and Rosen [17] supported the latter concept, their data showed that the cortical efferent zones overlapped extensively. Those zones projecting to the wrist overlapped in such a way that if a *chunk* of cortex in this area became uniformly active, antagonist muscle groups would be co-facilitated. Although this antagonist co-facilitation was not observed for the finger areas (perhaps

because EMG activity was not recorded) more than one muscle was always activated from a particular *chunk* of cortex.

The single muscle - single column hypothesis, as reviewed by Humphrey [25], soon ran into theoretical obstacles. Only the pyramidal cell axons of layer V were shown to project to subcortical sites [26], and more intense ICMS in the upper cortical layers is required to elicit motor responses. This would reduce the efferent column to a disk. Another problem lies in the selection of the cortical columns during a movement. Since multiple muscles are used in any movement and the combinatorial activity of the selected muscles is dynamic during the movement, the afferents selecting the columns to be activated would contain all the information required to activate the proper muscles at the correct intensities in the proper temporal sequence. This would require that all the kinematic and dynamic parameters of the movement be computed before the columns were selected. However, based on the movements elicited by activation of motor cortical afferent systems, this appears unlikely. Recording studies in behaving primates [27, 28] showed that adjacent cells often covaried with antagonistic muscles or muscles about different joints. Very few pairs showed a constant covariation with the activity pattern of the same muscle.

In addition to these shortcomings of the efferent zone concept, ICMS was shown to be a problematic technique. Jankowska et al. [29] showed that ICMS led predominantly to indirect, transynaptic activation of pyramidal tract cells. She and her colleagues compared the latency of an antidromic response recorded in layer V elicited by stimulation of the lateral funiculus to the orthodromically elicited descending volley recorded from the same site on the dorsolateral cord. The orthodromic volley resulted from either surface or intracortical stimulation. The ortho- and antidromic activation had comparable latencies with surface stimulation. However the predominant component in ICMS elicited volleys was of longer latency showing that the activation was transynaptically conducted to the corticospinal tract. This type of indirect cortical activation was also noted by Asanuma and Rosen [30] and most likely resulted from excitation of recurrent collaterals and/or interneurons. ICMS elicits activity over a wide area of cortex and it is likely (especially with repetitive stimuli) that this activates a complex cortical network that produces the inhibitory surround of the efferent zone. This activation pattern is not likely to resemble that which takes place during volitional movement. In fact, a recent report by Lemon et al. [31] found that unitary activity of neurons projecting from the motor cortex to hand muscles almost always facilitated muscle activity while ICMS at the same cortical site was more likely to produce suppression in the post-spike average of EMG.

Although the general somatotopic organization in the motor cortex represented by the inverted figurine on the convexity of the hemisphere is still a good anatomical summary, more recent mapping experiments in non- or lightly anesthetized monkeys dispute the original details of this organization. Murphy et al. [32] trained monkeys to relax their arm muscles and observed invariant movements in response to low intensity ICMS. They found that cortical loci from which movements could be elicited were organized in a nested manner. Those sites corresponding to movements of the most distal part of the arm were surrounded by successively more proximal movements. The areas corresponding to movements about adjacent joints were contiguous. A multiple representation of individual joint movements was found. Humphrey [25, 33] using ICMS and EMG recordings also found a multiple representation of muscles in the motor cortex. Low threshold sites that elicited activity in wrist flexors were coincident with those eliciting activity in wrist extensors. The same site also elicited cocontraction of elbow extensors and flexors. Thus activation of a wrist extensor and flexor as well as an elbow extensor and flexor could be elicited from the same low threshold site. The only observed movement at this site was wrist extension even though the other muscles were active simultaneously. These results were interpreted as support for the movement representation concept. During a natural movement, multiple muscles are simultaneously active and, for instance, when the fingers are moved the more proximal joints act to support the hand so that muscle contraction about multiple joints is also required. Thus activation of a given *chunk* of motor cortex results in simultaneous activity in a combination of muscles to yield a particular movement.

PHYSIOLOGICAL STUDIES

Bernstein, in 1935 [34], developed a set of arguments describing the interrelation of movement control and localization. These arguments were based on his detailed observations of human kinematics. He found that even in stereotyped repeated movements, such as with hammer pounding, that the trajectory of each repetition is different. Using a simplified equation of motion for a single muscle and joint, he showed that the displacement resulting from a single force impulse is dependent on the angle of the joint and its angular velocity. If the CNS is to generate displacement by generating muscular force, then the signal used to excite the muscle is also dependent on joint angle and velocity. The control signal must rely on proprioceptive information. Since the proprioceptive signal changes continually (dynamic environment) a static control signal would lead to

different movements each time it is repeated. In other words, to repeat the same movement a different control signal would need to be produced for each repetition. For example, as a hammer strikes a nail, the nail is displaced, altering the starting location for each repetition. If the same movement command was emitted, not only would the hammer miss the nail because the nail had moved, but with a constant stroke displacement the location of the termination of the return stroke would also shift as the nail was driven. Bernstein showed that the entire trajectory changed for each repetition and argued that the CNS must be able to calculate joint and external forces continuously.

Bernstein was interested in the "structural physiology" of movement. This was defined as the temporal pattern of the coordinated activity of multiple muscles across multiple joints during movement. He postulated that many central structures contributed to this control. Since the efferent activity of many structures projected to the spinal cord independently, this was a parallel scheme emphasizing not the activity of single neurons but the organization of their common features. Although he believed in the existence of localization, this was based on functional organization, not topology. "Thus, in the problem of localization what is important for our purpose is not precisely where in the cortex one or another peripheral object or function is reflected, but *what* is represented, and *how*." He further described the fallacy of movement representation in specific sites of the cortex ("push-button control board model"), arguing that since the efferent command for a movement must change at each instance, the structure underlying this control cannot be rigid. If individual muscles are represented in the cortex by a one-to-one mapping, then each repetition of the same movement would entail activation of different parts of the cortex since the muscle activation pattern differs for each repetition. Obviously the boundaries of the movement representation would have to change for each repetition. Muscle localization would deny movement localization and vice versa. "One of the two chess pieces must here be taken, and it is here a very pertinent question which of the two the old-fashioned localizationalist would rather sacrifice." The topographical organization of motor cortical neurons is not a relevant functional factor. Rather, the information contained within the neuronal activity and the way that it is distributed are the key features of motor control. It should be further emphasized that the demonstration of anatomical connectivity is not sufficient for elucidating functional distribution. Whether information from one cell is transmitted to another is a non-stationary, non-linear probability function that is determined by the total state of the system at a given point in time.

Very few studies have examined the neuronal substrate for reach to grasp

movements (see Gibson et al. this volume). I will review briefly the literature associated with single-joint, multi-joint and drawing movements. Finally I will discuss the studies that have examined the neuronal activity associated with grasping. The concept of functional localization has been an important issue as these behavioral paradigms have evolved. As we develop more natural paradigms and study the neuronal activity associated with them, our concept of *what* function consists of and whether it is localized in a single anatomical entity has also evolved.

Single-joint paradigms

Since few neurophysiological recording studies employed animals that actually moved, until the 1960s, knowledge of movement-related information contained in central structures was minimal. The first investigator to carry out an experiment in this regard, that was germane to reaching and grasping, was Evarts, who recorded single cell activity in the motor cortices of awake, behaving monkeys. His initial study [35] showed that most pyramidal tract neurons in the arm area of the motor cortex were active during spontaneous arm movement. Monkeys were trained to make alternating wrist extension-flexion movements against a telegraph key in his next study. The animals were cued by a signal light to make the movement. He found that the motor cortical neurons fired in response to the cue if the cue was associated with the movement. Although there was a loose relation between neuronal onset latency and movement onset, the correlation was "far from perfect". The neurons tended to respond prior to wrist EMG onset. These initial studies showed that many neurons from a wide topographical area responded for each movement and although their activity was clearly associated with the movement there was no obligatory linkage between the discharge pattern of individual neurons and the movement onset. A later study [36] addressed the question of whether the neuronal discharge was correlated to the force used to displace the limb or to the displacement itself. In this study, monkeys performed a wrist flexion-extension task against a handle that could be loaded to assist or resist the movement. In theory this was to dissociate force from displacement since the latter was the same in each trial while the force required to produce the displacement was varied by changing the load. Evarts intended to test the theory that the motor cortex acts as a displacement controller, specifying the position of the limb regardless of the force required to get it there. In this theory other CNS structures would transform the displacement signal into the appropriate muscle contractions. The results, however, supported the opposite conclusion. A neuron that fired as the wrist was flexed in the case when the handle was not loaded would

increase its discharge rate when the load opposed flexion and decrease when the load assisted flexion. This suggested that the cell was load sensitive and was not coding displacement or, in this case, wrist angle. The discharge pattern of the cells was similar to the EMG activity of the primary muscles used to flex and extend wrist. However, as the author pointed out, even for this relatively isolated wrist movement many muscles about the fingers, wrist elbow and shoulder are active simultaneously. This makes it difficult to ascertain to which specific muscle or combination of muscles the cell is **exclusively** related. In this type of experiment it isn't possible to completely dissociate force from displacement since a change in force is required to accelerate the handle during the movement. Examination of discharge rate and force showed that there was not a direct relation between the two variables. For instance, a cell that would start to fire as flexor force was applied to the handle would be silent as maximal flexor force was generated which coincided with the time that the handle was arrested by a mechanical stop. Although motor cortical activity was related to static force, the cell activity was also related to other parameters, such as the rate of change of force (dF/dt), and displacement.

In the following years, other investigators basically confirmed these findings using similar experimental paradigms. Humphrey et al. [37] modified the paradigm by requiring the monkey to terminate the movement in a target zone instead of against the mechanical stops. Using a small population of motor cortical responses they showed that this activity was related to force, velocity, position and dF/dt. The population response was constructed from the activity of three to eight simultaneously recorded cells and the spike frequency of each was weighted by a regression coefficient to the parameter being considered. This weighted factor was then summed with those from the other cells of the population and scaled before being compared to the time profile of the movement parameters. It was found that the correlation between the population response and a particular parameter increased with the number of cells in the population. The latency between the population response and, for instance, force, was found to be about 100 ms. Interestingly, the correlation between individual cells and a given movement parameter was quite labile and varied between trials. In agreement with Evarts, these investigators found force to be the parameter best encoded in the neuronal activity, but velocity and displacement were also well represented. Although the time course of force was well represented in a population of cells, when the load was changed, the coefficient for each cell had to be scaled. It was concluded that steady force was not well represented in the population. In contrast, a given set of coefficients calculated for velocity and displacement yielded accurate

predictions under various load conditions.

Schmidt et al. [38] modified the basic paradigm by replacing the weight and pulley loading system used in the previous studies with a torque motor, giving them the advantage of being able to change loads continuously without disturbing the monkey. The torque was adjusted to resist the movement in a spring-like manner and the movement divided into three portions: an initial hold, a transition and a terminal hold phase. They found that almost all the cells responded in the transition phase where the opposing forces reversed. Although the cells responded in this phase, the magnitude of their discharge was unrelated to the magnitude of the transition. This led the authors to conclude that the "motor cortex is involved in specifying the muscles to be activated for a given movement and not the level of force produced by these muscles."

Using a subset of motor cortical efferents, Fetz and Cheney [39] later reached a similar conclusion. They examined the responses of corticomotoneuronal cells (CMN) that were motor cortical neurons tested with spike-triggered averaging (STA - a technique that measures the influence of a spike on muscle excitability) and assumed to have monosynaptic connections with α motoneurons. Monkeys performed either an isometric wrist task or movements against an elastic load. The researchers found that although the average responses of these cells covaried with tonic force, the responses correlated poorly with the temporal profile of force.

Other investigators using single-joint movements found that motor cortical activity was related to joint displacement and stiffness [40, 41] and the expected direction of the next movement [41]. A recent study [42] compared the activity of cells in the putamen, supplementary motor cortex and primary motor cortex while static loads were applied to the arm in an elbow flexion-extension task. Cells that responded preferentially to load or the direction of displacement were found with equal frequency in all three structures. The lead time between the onset of activity to the start of the movement was shortest in the supplementary motor area, followed by the activity in motor cortex with the latest responses in the putamen. However there was a large overlap in these times so that many of these neurons were simultaneously active.

In general, these studies showed that the motor cortical activity of single cells was related in a complex manner to the production of force. All of these studies examined wrist torque resulting from a multitude of muscular activity throughout the arm. This line of experimentation originated by Evarts can be viewed historically as a transition from the long history of topographical localization toward the identification of relevant movement parameters represented in the motor cortex. The parameters examined with

these restricted movements were all mechanistically related to the physical properties of the rotating joint. As Bernstein suggested, these may not be the *what* that is represented in the activity of, in this case, the motor cortex. The concept of a higher order representation of the movement as a *behavioral output* was developed as investigators began to examine motor cortical activity in less restricted movements.

Multi-joint paradigms

As unrestrained arm movements began to be employed in cortical studies it became evident that simple parameters related to individual joints or muscles were not well represented by motor cortical activity. Although Evarts [35] described motor cortical activity as monkeys reached spontaneously, Porter and Lewis [43] reported the results of the first recording experiment where a multi-joint reaching task was used. Monkeys were trained to reach out, grasp and pull a spring-loaded handle. Pyramidal tract neurons recorded in the motor cortex were found to be modulated continuously throughout the task [43]. Different neurons appeared to be recruited for specific portions of the task. Unfortunately, individual neurons were not classified as to their somatotopic correspondence.

One of the first studies to detail both motor cortical activity and movement parameters during reaching was carried out by Murphy et al. [32]. They recorded motor cortical activity as monkeys reached forward to a control panel to push one of six buttons. The three-dimensional position and orientation of the arm was measured throughout the task with an optoelectronic device and joint angles about the shoulder and elbow were calculated. The researchers found that there was no simple relation between EMG patterns of the major arm muscles and motor cortical activity. Pairs of single cells that responded to joint rotation in opposite directions were more reciprocal in their activity patterns than supposedly antagonist muscle pairs about the same joint. Although shoulder-related motor cortical units consistently varied their discharge patterns for movements to the different targets, their activity patterns were not related to a particular joint angle profile. It was concluded that "the production of any movement, however complex or discrete it may seem peripherally, engages a complex population of precentral neurons, such that any one neuron may behave similarly for overtly different movements."

At the same time, Georgopoulos et al. [44, 45] were recording motor cortical activity as monkeys performed two-dimensional reaching movements by moving a manipulandum over a planar work surface. The task required that the animal move the manipulandum from a center start target to one of

eight equally spaced targets that formed a circle around the start location (center→out task). The movement parameter examined in this work was direction. Movements in different directions require changes in multiple joint angles and muscles. Despite the underlying mechanical complexity of the movement, a simple relation between discharge rate and movement direction was found for most of the precentral cells that were active in the task. The relation between discharge rate and direction was described with a cosine formula that spanned all movement directions. The *preferred direction* of a given cell was the movement direction that corresponded to the peak discharge rate. Thus each cell's activity encoded all movement directions. Such coarse coding of a movement parameter is somewhat contrary to the "push-button control board" concept of motor control. Instead of specific cells active only in a narrow range of movement direction, many cells in the motor cortex are simultaneously active, encoding each movement direction as a population. A vector algorithm [45, 46] was developed to describe the emergent directional information represented in this population. Each cell's average discharge rate was calculated for a movement to a specific target. This rate was used to scale a unit vector in the cell's preferred direction. This operation was carried out for movements to each target and for each cell in the population. The resulting contributions from each cell to the population was illustrated as a cluster of vectors pointing in different directions. The vectors representing cells whose preferred direction coincided with the movement direction tended to be longest and the vector resulting from summing the contributions, the *population vector*, pointed in the direction of the target for each of the movements.

This approach was shown to be valid for the more general case of arm movements through free space [47-49]. Monkeys were trained to reach from the middle of a cube to each of its corners and the resulting single-cell activity could be described with a tuning volume based on the cosine function. Population vectors again closely predicted the movement direction. When the population vectors were calculated at 100 intervals throughout the time course of the movement, it was evident that the population vectors appeared and pointed in the movement direction about 60 ms after the presentation of the movement stimulus which was 120 - 140 ms before the movement began. This showed that the directional information in the motor cortex was predicting the movement direction well in advance of the actual movement.

The population vector algorithm has been used to better understand what type of information is represented in the motor cortex. A clear dissociation between cortical and muscle activity was demonstrated in the 3D task [50]. A set of parallel movements between the buttons on the front of the cube

showed that single cells had similar discharge rates for movements in the same direction carried out in different portions of the workspace. EMG activity recorded for the same movements was quite different. The neuronal response seemed to code direction relative to the initial position of the hand regardless of its location.

If direction is coded instantaneously in the activity of motor cortex cells, it should be possible to predict movement direction continuously throughout a movement. This was tested in an experiment where monkeys drew sinusoids [51]. Direction changed continuously as the figure was drawn. The discharge activity of single cells changed through the task in a way that corresponded to each cell's tuning function. The directional activity of these cells coded for a direction of movement that occurred with a latency of about 120 ms. A portion of the discharge activity also was related to movement speed (the speed of the movement also changed continuously). This speed coding was most evident for movement directions near each cell's preferred direction.

A time series of population vectors calculated from this activity showed that the population activity corresponded to the tangential velocity of the drawing movement [52]. The direction of each population vector corresponded to the continuously changing movement direction while the magnitude of each vector was well correlated to the movement speed. The relation between the length of the population vector and movement speed was due to the direction dependence of speed coding in the activity of individual cells. Cells tend to make large contributions to the population vector if their preferred directions are near the movement direction. These contributions will be reduced for low speeds in the preferred direction and enhanced for high speeds. Reduced contributions in the direction of movement tend to make the cluster of constituent vectors more symmetrical and this results in a shorter population vector. The constituent vectors are longer for higher speeds when the movement is in their preferred direction and results in more asymmetrical clusters and longer population vectors. Thus both direction and speed are parameters that emerge from the population. This is a good example of how multiple parameters may be simultaneously encoded in the same cell population.

These results also confirmed those findings suggesting that the information represented in motor cortical activity is related in an *instantaneous* way to the ongoing process of movement. Since the population vectors are well correlated to tangential velocity, the population activity codes for trajectory on a piecewise basis. The origin of each vector is spatially aligned with the tip of the previous vector. The vectors code for direction and speed relative to this origin.

These results show that the trajectory of the arm is well represented in the population activity. This seems to contradict the findings of Evarts showing that force rather than hand position was represented in the activity of single motor cortical cells. Besides the obvious differences between the experimental tasks these findings might be explained if populations are considered. As outlined earlier, even these original experiments were unable to resolve a clear relation between force and discharge rate. Humphrey et al. [37] found that the combined activity of a small group of motor cortical cells was well related to the applied load in this type of behavioral paradigm. It is important to note that a kinematic parameter, velocity, was almost as well related to the neuronal activity.

Investigations that considered direction as a parameter have yielded insights into this issue. Kalaska et al. [53] used a two-dimensional manipulandum that could be loaded in different directions. Monkeys performed the center→out task with the loaded manipulandum. Loads applied in a direction opposing the motor cortical cells' preferred directions tended to increase the activity. The directional tuning curve did not change shape when loads were applied, rather the entire curve shifted along the axis representing discharge rate. Thus the static load seemed to bias the directional tuning curve and both parameters were simultaneously represented in a given cell's discharge rate.

Isometric tasks where force is exerted in the absence of displacement is the only situation where these variables are completely dissociated. Georgopoulos et al. [54] have shown how motor cortical activity is related to force in this condition. Monkeys were trained to exert a force pulse on a handle in response to a set of targets on a computer monitor. Force feedback was provided by a cursor on the monitor. The eight targets around a center start position were arranged in the same way as those of the center→out task. As previously shown for non-isometric movements, the discharge rate of these motor cortical cells was broadly tuned to the direction of force. A constant bias force could be introduced by altering the relation between the cursor and the applied force, so that the subject was required to generate different directions of force, depending on the bias, to move the cursor in the same direction. The shape of the tuning function was unaffected by the bias force. The investigators considered net force to be the difference between the force generated by the subject and the bias force. The population vectors corresponded to the net force. In a different part of the analysis, the change in force between ten millisecond bins was found to be similar to the net force when calculated continuously as a time series of vectors. A time series of population vectors calculated for each bin matched a corresponding sequence of net and force change vectors which coincided

in direction with a visually derived intention vector. These were clearly different from the total and bias forces. The authors point out that although the mechanical factors and EMG are quite different in the moving and isometric tasks, the underlying motor cortical activity is very similar and may relate "to an abstract representation of spatial trajectory", a conclusion supported by the drawing study [52]. The activity in the motor cortex seems to be related to behavioral conditions and is somewhat removed from the physical and mechanical constraints of the task.

Two sets of experiments support the role of the motor cortex in abstract processing. One set relates to the invariant rules subserving drawing. Objects are drawn in segments defined by a zero-crossing in acceleration. For instance, figure eights are generally drawn in two segments with each loop of the eight defined as a segment [55, 56]. Monkeys were trained to draw figure eights on the touch screen and single motor cortical units were recorded during the task [57]. The animals produced the same segmentation as humans. Population vectors calculated through the task were added tip-to-tail producing a neural representation of the trajectory. This neural trajectory had the same segmentation as the actual movement showing that this behavioral invariant was encoded in the activity of motor cortical cells. Another invariant, the isogony principle, was also tested. This rule was originally found in handwriting [58] and showed that angular velocity was directly related to the radius of curvature. Subjects slow down in more curved regions of the drawing. This was tested on monkeys trained to draw spirals. These animals produced the spirals obeying the isogony principle and the neural trajectory derived from their motor cortical activity also followed this rule. The invariants derived from drawing movements are incorporated into the activity of the motor cortex, suggesting that the behavioral aspects of the task are an important factor represented in the output of the motor cortex.

An example of the cognitive role that the motor cortex can play in the processing of spatial information was provided in an experiment where a monkey was required to perform a spatial transformation [59]. This experiment employed a variant of the two-dimensional center→out task where the monkey was required to move 90° counterclockwise to the illuminated peripheral target. For example, if the target appeared at the two o'clock position, the animal was required to move the manipulandum to the 11 o'clock location. Population vectors, calculated at two millisecond intervals, initially pointed in the direction of the illuminated target early in the reaction time. They then rotated toward the counterclockwise location until reaching the 11 o'clock position about 35 ms before the animal began to move at this target. This response took place during the reaction time, in the absence of

movement, and is a further illustration of how a population of motor cortical cells may subserve the higher-order processing associated with the performance of spatial motor tasks.

Grasping studies

The pyramidal tract and motor cortex have long been established as critical structures for precision grip. This conclusion has been reached using lesion studies [60-65]. The common result of this work is that there is a permanent inability to form a precision grip using the thumb and index finger. Another conclusion from experiments using split-brain monkeys is that there is a dichotomy in the mechanisms used for grasping (distal) from those used for reaching (proximal). Vision-supplied information to the contralateral cerebral cortex is required for grasping, but is not necessary for reaching [66, 67]. Differential control using peripheral and foveal visual fields for the transport and target acquisition phases of pointing movements has also been found [67].

Recording experiments also suggest that motor cortical cells are involved in regulating precision grip. This has been shown in isometric tasks where there is a monotonic relation between force and discharge rate especially for low ranges of force [68, 69]. However, although these cells were thought to be corticomotoneuronal projections based on post-spike facilitation, there was poor correlation between firing rate and EMG in the target muscle during maintenance of static force. Only a few cells were found where there was a high correspondence between discharge rate and grip force. Surprisingly, about the same number of neurons that showed an increasing monotonic relation showed a decreasing relation between grip force and discharge rate. It was hypothesized that the cells with negative correlation may recruit motor units that generate smaller forces. Another study by these investigators [70], shows that the post-spike facilitation of this projection is task dependent. Monkeys performed either a precision grip or a rotation with their index fingers and thumbs. A "dramatic" difference in the post-spike facilitation was found in the two tasks.

The control of precision grip is most certainly aided by vision in normal behavior. Cells responsive to both visual input and motor aspects of manipulation have been recorded in the posterior parietal cortex [71, 72]. These responses were studied quantitatively as monkeys manipulated different objects in light and dark conditions [73]. Neurons were found to be active during manipulation in the dark (hand movement units), only in the light (visual dominant units) or responsive in the dark with an increased response in the light (visual and motor units). The animals were trained to

manipulate a variety of objects and each neuron tended to be preferentially active during a particular manipulation. It was suggested that integration of motor and visual information takes place in this cortical area. Visual afferents from extrastriate visual cortical areas (i.e., parietal-occipital and middle temporal) terminate in this region. There is also a reciprocal connection with premotor area 6. This region of area 6, on the posterior bank of the arcuate sulcus, has direct projections to the motor cortex and is another site where neurons responsive to grasp have been found [74].

Although, detailed studies examining neurophysiological activity during reaching *and* grasping have not yet been carried out, the results of the gripping experiments are quite similar to those for reaching. Many structures are active simultaneously. Posterior parietal, arcuate premotor and motor cortex seem to be part of a circuit that utilizes visual information during manipulation. Behaviorally, there is an apparent dichotomy between the use of the proximal joints to transport the hand to the target and the actual grasp of the target. It should be noted that these phases overlap since pre-shaping of the hand occurs during the transport phase. Similarly, the motor cortex, in addition to the cells projecting to distal motor pools, contains many cells related to the displacement of the proximal arm segments and the activity of these cells accurately reflects the arm's trajectory. Interestingly, these cells, although related to proximal joint displacement, may, as a population, encode the trajectory of the hand better than that of the more proximal segments [75, 76].

It is difficult to assign a specific function to the motor cortex, even though ablation of this cortical region leads to a loss of precision grip. In the one study [43] that looked at reaching and grasping, motor cortical neurons were "recruited" continuously throughout the task, that is, it was not possible to conclude that activity in this structure was related to grasping exclusive of reaching. An anatomical study [77] employed ICMS to determine motor cortical somatotopy and small HRP injections to identify cells projecting to the injection site. Wide spread interconnectivity between different parts of the forearm representation was found. Injections made at a site where ICMS elicited thumb movement were found to label cells at sites where elbow, wrist and shoulder movements were elicited. The HRP was transported by horizontal axons in layers III and V. These findings were interpreted as evidence that activity within the motor cortex is distributed and helps to explain how simultaneously active cells communicate. This also argues against the idea that individual cells are controlling aspects of movement (i.e., single muscles) in isolation.

Thus, as with reaching, it is likely that different neurons within the motor cortex are transmitting information related to different aspects of gripping

and that the information content within a given corticifugal axon is task dependent [70]. To consider these neurons as controllers of muscle groups is also nebulous since few neurons were simply correlated to total force. It will be necessary to consider the simultaneous action of many neurons within the same structure and the distributed activity of different structures before the nature of the control process can be understood. As we have begun to show with the reaching studies, it is likely that the cerebral processing associated with reaching and grasping is composed of information related to the cognitive strategies used to achieve the behavioral goal in addition to the control of specific mechanisms employed to produce the movement.

CONCLUSION

Historical concepts tend to resurface in cycles. Until the 1800s the cerebral cortex was considered to be removed from the mechanics of somatic function and to house what philosophers called the "vital force". The cerebral cortex was not thought to be electrically excitable until the work of Fritsch and Hitzig and the demonstration of intrinsic current by Canon in the 1870s. Although the conceptual roots of localizing theory can be traced to the ancient Greeks, it was this period in the late 1800s that ushered in the foundations of what we consider to be cerebral localization. As illustrated by the motor cortex, our understanding of cerebral function was driven by successive technological advances. Just as the development of the electrochemical cell and its application to biology by Galvani led to the discovery of the essential nature of the reflex arc by Mueller and the development of the galvanometer made it possible for du Bois-Reymond to describe the action potential, the experiments of the 1870's led initially to a rapid establishment of the motor cortex as a "push-button control board" for motor control. These ideas were to remain deeply established for more than a century. Most of the experiments supporting this concept relied on the notion that one *chunk* of cortex was active to the exclusion of others. Another nuance of this reasoning was that all cells in a particular *chunk* were active simultaneously. The controversy this elicited was whether all the cells in a *chunk* were coding for activation of the same muscle or coding for different muscles all involved in the same movement. It was not until moving subjects were studied that this controversy became a non-issue.

In fact, Bernstein, who developed a cinematic technique to measure human movements in three-dimensional space, argued against this type of localization in the 1930s. The development of chronic recording in monkeys by Evarts made it possible to study actual arm movements as motor cortical

A.B. Schwartz

activity was recorded. In this transition out of the localization era these first chronic experiments examined only single-joint movement and their results were unclear. The muscle versus movement controversy was still unresolved. As the experimental paradigms advanced to movements in two-dimensional followed by three-dimensional space, it became clear that higher order movement descriptors such as direction and trajectory were represented in the activity of motor cortex. Insights from cognitive experiments have shown that neural activity subserving spatial problem solving takes place in the motor cortex. These experiments are transforming our ideas of the motor cortex away from connectionist dogma toward an understanding of how complex distributed systems control the behavioral expression found in such acts as reaching and grasping. Perhaps our understanding of cortical processing is evolving toward a more philosophical description of the complex and *vital* way we behave in our surroundings.

ACKNOWLEDGEMENTS

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