

the Intelligent Movement Machine

An Ethological Perspective
on the Primate Motor System

Michael S. A. Graziano

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MICHAEL S. A. GRAZIANO, Ph.D.

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Preface

In 1870, Fritsch and Hitzig discovered the motor cortex in the dog brain. Since then, for one hundred and thirty years, researchers have grappled with the fundamental question of motor cortex: How is it organized?

I believe this question is finally answered. The answer is simple in concept. An animal's normal movement repertoire is flattened onto the cortical surface. The complexity of the map comes from the complexity of the movement repertoire. With a good description of the typical movement repertoire of a species of animal, it should be possible to predict mathematically the layout of the motor cortex. We now have an approximate description of the movement repertoire of macaque monkeys, and with it we can explain the overarching organization of the monkey motor cortex.

The theory that the motor repertoire is flattened onto the motor cortex is one specific example of a general principle of brain organization. One might say that the mental repertoire of the animal is mapped somehow onto the entire brain. In the case of movement, the repertoire is conveniently observable and therefore its mapping onto the cortical surface can be studied directly. The purpose of this book is to review experiments on how the motor repertoire is mapped onto the cortex, ranging from the initial discovery of motor cortex to the present.

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Chapter 1

Introduction

BACK STORY: MIXING TWO EXPERIMENTAL CULTURES

When I was a postdoc at Princeton University, I worked on the integration of vision, touch, and movement in the monkey brain. The experiments involved monitoring the activity of single neurons in the motor cortex during the monkey's movements or during the presentation of sensory stimuli. I had never considered using electrical stimulation to study motor cortex. Many colleagues had suggested the technique, and my response was something like, "You get muscle twitches. Big deal. You can't really learn anything."

At the same time another postdoc in the lab, Tirin Moore, had begun a set of experiments on the frontal eye field of monkeys. He used a common electrical stimulation technique in which pulses of current are delivered into the cortex through a fine, hair-like electrode. The pulses are presented in a train at high frequency (typically 200 pulses per second). This method directly activates a small sphere of brain tissue around the electrode tip. The directly stimulated neurons then recruit physiologically connected networks. If stimulation is applied to a spot in the frontal eye field, it evokes an eye movement that closely resembles a natural one.

When experimenting on the frontal eye field, for each new monkey studied, one typically first explores a broad area of cortex, stimulating in a variety of locations to find the borders of the area of interest. During one such exploration, Tirin came running down the hall to my office, his lab coat billowing behind him like the cape of a superhero, and said, "Mike, you have to look at this." I came and looked.

He held a button in his hand, and every time he pressed the button, the monkey sitting in the plastic monkey chair in the center of the room extended his arm forward and shaped his fingers as if reaching for something invisible. The effect was immediate, consistent, and obviously as amazing to the monkey as it was to us because the monkey grabbed hold of his hand with the other one, pulled it straight down, and sat on it, effectively ending the experiment for the day. Tirin had obviously missed the frontal eye field and gotten the electrode into the primary or premotor cortex.

"We have *got* to study this," he said.

The evoked movement was no muscle twitch. The reason was immediately obvious to us. In a standard stimulation experiment on motor cortex, the stimulation is applied in a brief burst for 50 ms or less. The result of this brief stimulation is a muscle twitch. But little if any behavior unfolds on such a short

time scale. Neurons in motor cortex are not normally active in 50 ms bursts but instead, to a first approximation, are active throughout the duration of a movement. In the present case, the stimulation was applied for half a second, approximating the duration of a monkey's reaching or grasping. As a result, instead of a muscle twitch, a complete movement unfolded.

After a month of mulling and of dinner conversations at the local Italian restaurant, three of us began the new experiment: Tirin, myself, and Charlotte Taylor, a graduate student also in the lab. We set out to study the motor cortex using the technique of stimulating on a behaviorally relevant time scale.

Our procedure was to sit for hours in front of the monkey like a panel of judges, studying one cortical site in a day, stimulating it hundreds of times under every condition we could think of, watching every event, discussing every detail, and arguing over exactly what description to write in the data book. In addition to our general contributions to the experiment, we each had specific duties. I was the scribe. Charlotte operated the button that delivered the stimulation to the cortical site. Tirin fed the monkey a constant supply of raisins to calm him and entice his arms into a variety of test configurations (The monkey eventually became obese from the constant snacking.). The study was intentionally as unstructured and as observational as possible. We did not know what to expect.

On the first day that we reached the motor cortex it became abundantly clear that stimulation evoked complex movements combining many joints. We were able to evoke integrated movements of the shoulder, arm, and hand. We also noticed that regardless of the starting position of the arm, the movement evoked by stimulation seemed to bring the hand toward the same final position as if in a goal-directed action.

A few days later we encountered a site in the cortex where stimulation caused the fingers to close in an apparent grip, the hand to move to the mouth, and the mouth to open. The monkey appeared to be feeding himself, even though there was nothing in his hand. The movement was so natural, so utterly like the monkey's normal feeding action, that triggering it by button push gave us the willies. It was uncanny. We ran out of the experiment room and searched the halls for someone, anyone, to look at the result and tell us that it was real, that we weren't nuts.

We wondered if the monkey was inadvertently fooling us. Perhaps the stimulation caused merely a general tendency to move and the monkey then supplied a movement that was on his mind, so to speak, because he was constantly feeding himself raisins. This explanation seemed unlikely because we evoked the hand-to-mouth movement only from one region of cortex, and the evoked movement had a mechanical reliability. However, we tested the possibility by injecting an anesthetic into the monkey and waiting until he was asleep. Stimulation of the same site in cortex still drove the fingers into a grip, the hand upward toward the mouth, and the mouth open. The movement had nothing to do with the monkey's behavioral context. It was as mechanical as clockwork. We appeared to have tapped into its control mechanism.

As the experiment continued, we uncovered more actions that looked like they were straight out of the monkey's natural repertoire and that could be generated by stimulating specific sites in the motor cortex. Different zones within the motor cortex appeared to emphasize different major categories of action. Some of these action categories are illustrated in Figure 1-1. They included ethologically relevant behaviors such as closing the hand in a grip while bringing the hand to the mouth and opening the mouth; extending the hand away from the body with the grip opened as if in preparation to grasp an object; bringing the hand inward to a region just in front of the chest while shaping the fingers, as if to manipulate an object; squinting the facial muscles while turning the head sharply to one side and flinging up the arm, as if to

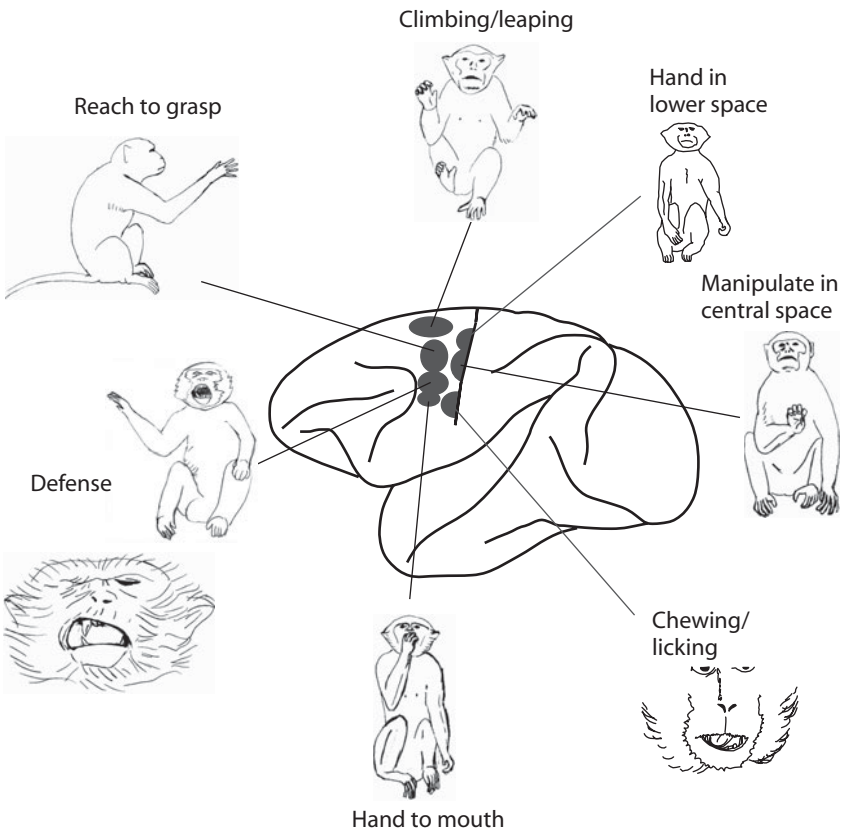


Figure 1-1 Action zones in the motor cortex of the monkey. Seven common categories of movement evoked by electrical stimulation of the cortex on the behaviorally relevant time scale of 0.5 sec. Images traced from video frames. Each image represents the final posture obtained at the end of the stimulation-evoked movement. Within each action zone, movements of a similar behavioral category were evoked. Based on results from Graziano et al. (2005; Graziano, Taylor, et al., 2002).

protect the face from an impending impact; and moving all four limbs as if leaping or climbing. The behavioral repertoire of the animal seemed to be rendered onto the cortical sheet. One might say that the cortical motor system had an action map.

The evoked movements were also roughly arranged across the cortex according to the location in space to which the movement was directed. The height of the hand was most clearly mapped across the cortical surface. Stimulation of the lower (ventral) regions of cortex commonly drove the hand into upper space, and stimulation of upper (dorsal) regions of cortex commonly drove the hand into lower space (Figure 1-2). Again, an important aspect of the animal's action repertoire was mapped across the cortex.

Over the next several years, as I set up my own lab at Princeton, we studied these cortical action maps with a variety of methods. We measured arm movement at high resolution to better understand the electrically evoked actions. We chemically activated or inhibited neurons at sites in the cortex and measured the effect on the monkey's behavior. We measured the neuronal activity in motor cortex that occurs during spontaneous movement to determine if the neurons are naturally tuned to complex actions. We even carried a video camera to the zoo, and then to an island populated by wild monkeys, to better understand the natural simian movement repertoire.

This line of experiments led us to propose two principles to explain the basic properties of the motor cortex. One principle concerned the topographic layout of the motor cortex, and the other concerned the neuronal mechanism by which motor cortex caused movement.

Topographic Organization

A traditional view of the motor cortex is that it contains a map of the body. This map was famously depicted by Penfield, whose homunculus diagram is shown in Figure 1-3. This traditional topographic scheme, however, does not capture the actual pattern of overlaps, fractures, re-representations, and multiple areas separated by fuzzy borders. The homunculus does not adequately describe the topographic organization. A current view of the motor cortex is that it can be divided into many distinct areas with separate functions (Figure 1-4). Yet the functions are largely not known, and the properties described thus far tend to vary across cortex in a graded fashion without hard borders. Rather than a set of separate areas, the pattern resembles a statistical distribution with clustering. Labeling those clusters with acronyms, drawing borders around them, and assigning functions to them may provide a convenient description but does not explain the principles behind the organization.

Based on our stimulation results, we proposed an underlying topographic principle for the motor cortex: the reduction of the many-dimensional space of the animal's movement repertoire onto the two-dimensional surface of the cortex. This reduction is similar to the problem in cartography of reducing the three-dimensional, curved globe onto a two-dimensional map, introducing unavoidable distortions and fracture lines. In the case of motor cortex, however,

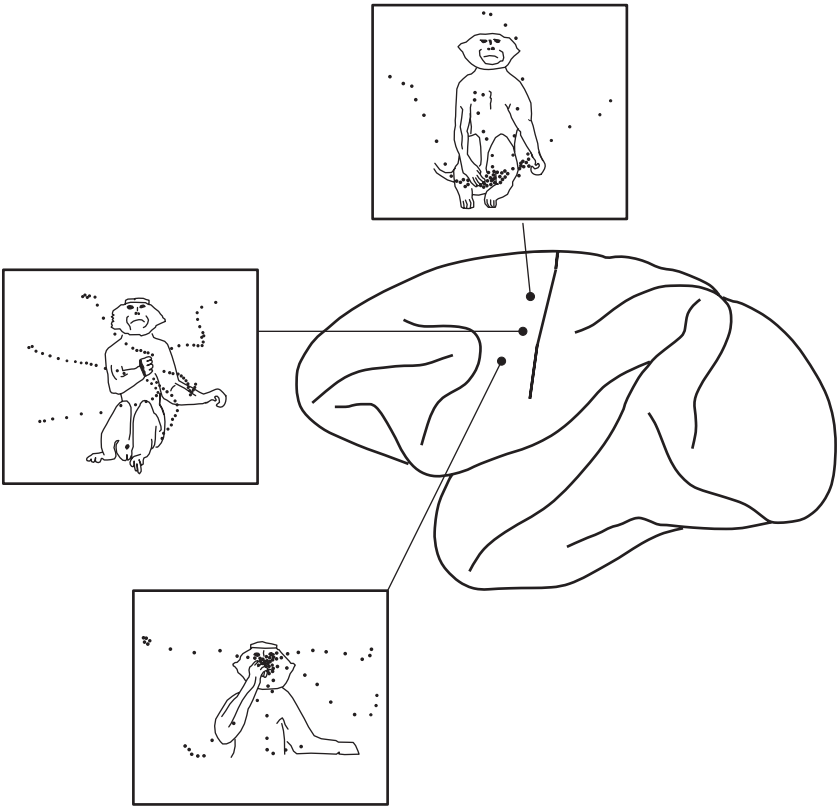


Figure 1-2 Progression of spatial locations to which hand movements are directed. Within the arm representation of the monkey motor cortex, electrical stimulation in dorsal cortex tended to drive the hand into lower space; stimulation in ventral cortex tended to drive the hand into upper space; stimulation in intermediate cortical locations tended to drive the hand to intermediate heights. Each image is a tracing of the final posture obtained at the end of a stimulation-evoked movement. Each dotted line shows the trajectory of the hand during the 0.5-sec stimulation train. Dots show the position of the hand in 30-ms increments. These trajectories show the convergence of the hand from disparate starting locations toward a final location. Adapted from Graziano, Taylor, et al. (2002).

the reduction is from the highly dimensional action space of the animal's normal behavioral repertoire to the two-dimensional cortical sheet. The core of this theory of cortical organization is that local continuity is preserved as much as possible. Information processors that need to interact are arranged physically near each other in cortex, presumably gaining a connective advantage. One could term this principle of cortical organization the rule of "like attracts like." Perfect continuity is not possible, however, because of the unavoidable difficulties of rendering a highly dimensional space onto a two-dimensional sheet. The result is a complex compromise among many constraints.

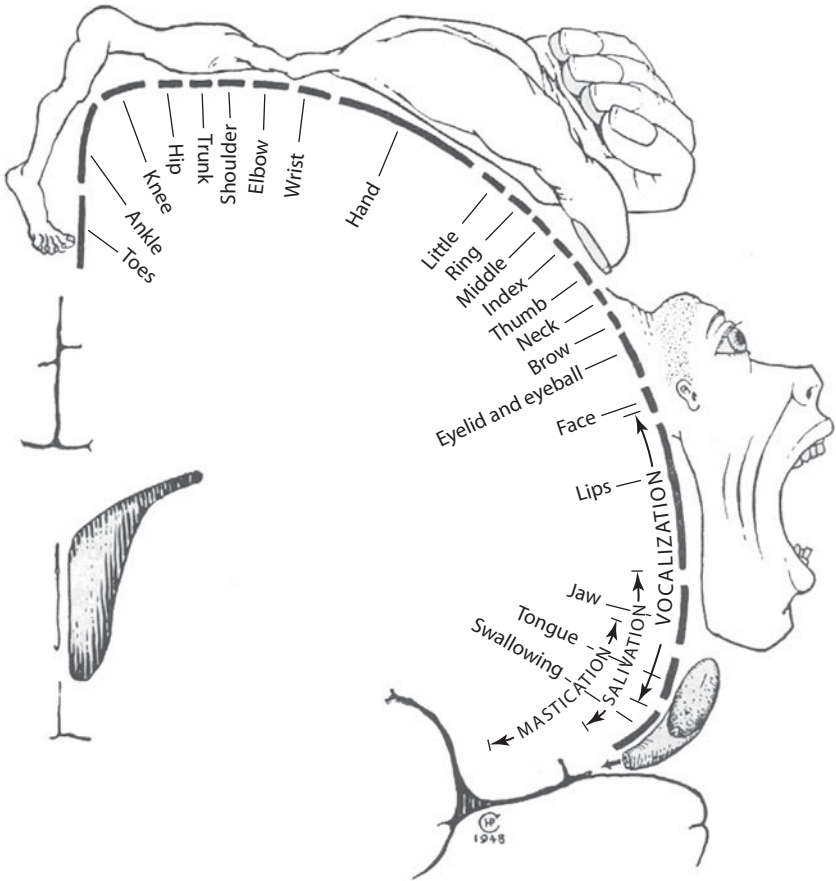


Figure 1-3 The motor homunculus of the human brain from Penfield and Rasmussen (1950). A coronal slice through the motor cortex is shown. Each point in motor cortex was electrically stimulated and the evoked muscle twitch was noted. Although each cortical point could activate many muscles, a rough body plan could be discerned.

In our proposal, the map of actions in Figure 1-1 is not by itself correct. It is present in the data, but the pattern is noisy and approximate. The map of hand locations shown in Figure 1-2 is also noisy and approximate, and therefore not by itself the correct description of motor cortex topography. The map of the body shown in Figure 1-3 is also present only in a rough sense and does not capture the complexities of the pattern. The proposal here is that all of these potential ways to organize movement, and perhaps others, are rendered onto the cortical sheet simultaneously, resulting in a compromise that does not neatly follow any single mapping dimension.

To test the validity of this theory of motor cortex organization, we used a mathematical model that collapsed an approximate description of the monkey's

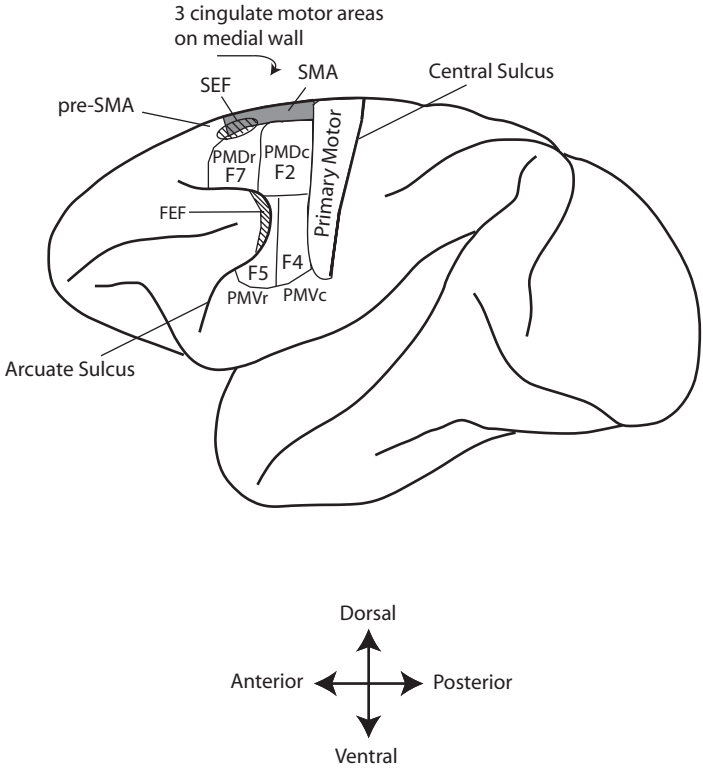


Figure 1-4 Some commonly accepted divisions of the cortical motor system of the monkey. PMDr = dorsal premotor cortex, rostral division, also sometimes called “Field 7” (F7). PMDc = Dorsal premotor cortex, caudal division, also sometimes called “Field 2” (F2). PMVr = Ventral premotor cortex, rostral division, also sometimes called “Field 5” (F5). PMVc = Ventral premotor cortex, caudal division, also sometimes called “Field 4” (F4). SMA = supplementary motor area. SEF = supplementary eye field, a part of SMA. Pre-SMA = pre-supplementary motor area. FEF = frontal eye field.

movement repertoire onto a two-dimensional sheet following the principle of maximizing local continuity (Affalo and Graziano, 2006b; Graziano and Affalo, 2007). The topographic organization generated by the model resembled the organization of the actual cortical motor system in many respects, including a rough clustering of movement categories as in Figure 1-1, an approximate mapping of hand position as in Figure 1-2, the outlines of a body map as in Figure 1-3, and the outlines of a primary motor area, dorsal and ventral premotor areas, supplementary motor area, frontal eye field, and supplementary eye field as in Figure 1-4. The theory of a dimensionality reduction was astonishingly

successful in explaining the overarching organization of this large swath of cortex totaling about 20% of the macaque cortical mantle.

Mechanism of Movement Control

A traditional view of the neuronal machinery of movement control is that activity at a site in motor cortex propagates down a fixed pathway through the spinal cord, activating a set of muscles. Based on our stimulation results, however, the underlying mechanism seems to be less of a simple feed-forward pathway and more of a network. The effect of the network is to create a specific class of mapping from the cortex to the muscles, a mapping that can change continuously on the basis of feedback about the state of the periphery. If the periphery is relatively still, the mapping from cortex to muscles appears fixed and resembles the traditional view. But once the state of the periphery is allowed to vary as in natural movement, the mapping from cortex to muscles becomes somewhat fluid in a manner that facilitates complex movement control.

For example, when stimulation causes the hand to move to the mouth, different patterns of muscle activity are generated depending on the starting position of the limb. If the arm starts to the right of the mouth, stimulation evokes activity in the shoulder muscles appropriate for pulling the arm toward the left. If the arm starts to the left of the mouth, stimulation evokes muscle activity appropriate for pulling the arm toward the right. In effect, the mapping from the stimulated site in cortex to the muscles is not fixed. It changes depending on feedback information about the position of the limb. In this manner, the network can control limb position.

In general if the network receives feedback information about a specific variable, such as hand direction, or hand speed, or the posture of the arm, then the network can learn to control that variable. A network of this type is not limited to the control of one movement variable. It can in principle control muscle force directly and also control higher order variables, in combinations required for the performance of specific actions. A formal neural-network model that incorporated this principle of “feedback remapping” was able to control a model arm, successfully generating actions similar to those evoked in our stimulation experiments.

Theoretical Framework

The computational studies summarized above on topography and mechanism provide a potential theoretical framework for understanding at least the outlines of the motor cortex. In this framework, the purpose of the motor cortex is to control behaviorally useful actions in the motor repertoire; its complicated topographic organization is the result of a systematic rendering of the motor repertoire onto the cortical sheet; and the neuronal pathways between cortical neurons and muscles are designed to support the multijoint, feedback-dependant movements common in normal behavior. The goal of the present book is to elaborate on this theoretical framework.

ORGANIZATION OF THE BOOK

The book is divided into two parts. The first part, ending in Chapter 6, reviews the previous literature from the discovery of motor cortex to the present, placing the current proposals into context. Any theory must be able to account for past results. By the same token, one cannot reject a theory because it fails to account for a distorted or mythological version of past results. One purpose of this review, therefore, is to lay to rest some of the common motor cortex myths, such as the myth of a muscle-by-muscle map. Chapter 6 discusses some advantages and limitations of the electrical stimulation technique because much of our work is based on this technique.

The second part, beginning with Chapter 7, describes the experiments and computational models that form the basis of the present perspective on motor cortex. Much of this work has been reported piecemeal in published articles. The present format allows for a more coherent global picture, additional analyses and results, and an extended discussion. Two chapters in particular are at the heart of the present story. Chapter 10 describes the proposal that the spatial layout of the cortical motor system can be understood as a reduction of the movement repertoire onto the cortical sheet. Chapter 11 describes the proposal that the mechanism of movement control by the motor cortex can be understood as a feedback-remapping mechanism, a divergent mapping from neurons in cortex to muscles that is continuously remapped based on information about the changing state of the periphery.

The final chapter of the book discusses possible links between motor control and social behavior, including the link between defensive movement and social smiles and between autism and abnormal movement control. The purpose of this final chapter is to emphasize the point that the motor system is not merely for activating muscles. It is a machine that allows intelligent interaction with the environment.

NOTE ON TERMINOLOGY

Figure 1-4 shows a schematic side view of a monkey brain with some commonly recognized cortical divisions (e.g., Dum and Strick, 2002; He et al., 1995; Luppino et al., 1991; Matelli et al., 1985; Matsuzaka et al., 1992; Preuss et al., 1996; Rizzolatti and Luppino, 2001). The cortical areas directly involved in motor control are typically divided into a lateral motor strip (unshaded in the figure) and a medial motor strip (shaded and partly hidden over the crown of the hemisphere). The lateral motor strip is divided into a posterior strip termed the “primary motor cortex,” and an anterior strip termed the “lateral premotor cortex.” The lateral premotor cortex is subdivided into a dorsal premotor area (PMD) and a ventral premotor area (PMV). In the monkey brain, each of these in turn is subdivided into a rostral area and a caudal area: PMDr, PMDc, PMVr, PMVc. These areas have also been labeled by Matelli et al. (1985, 1991) (in the same order) F7, F2, F5, F4. Because different groups have tended to publish work on different subdivisions, the PMDs are most often

termed “PMDr” and “PMDc,” whereas the PMVs are most often termed “F5” and “F4.” A region with distinct properties that probably corresponds to the dorsal-most part of F4 has also been termed the “polysensory zone” (PZ) (Graziano and Gandhi, 2000). In the human brain, the divisions between rostral premotor and caudal premotor are less well established and the homology to the monkey brain is not yet clear.

The medial motor strip (shaded in the figure) was originally labeled the supplementary motor area, or SMA (Penfield and Welch, 1951). However, this region has now been subdivided into SMA, pre-SMA that lies directly anterior to SMA (Matsuzaka et al., 1992), and in the monkey a set of at least three little-studied areas on the medial part of the hemisphere buried in the cingulate sulcus, that are termed the “cingulate motor areas” (Dum and Strick, 1991).

Two gaze-control areas are also shown in cross-hatching in Figure 1-4. The frontal eye field (FEF) lies directly anterior to the arcuate sulcus and in its anterior bank. The supplementary eye field (SEF) lies within the anterior part of SMA. Both of these gaze areas are defined by the eye and head movements that can be evoked by electrical stimulation. Eye movements can also be evoked to a lesser extent from PMDr and PMDc (Bruce et al., 1985; Fujii et al., 2000).

The term *premotor cortex* is used to refer to at least three different regions. First, it has sometimes been used to refer to the lateral premotor cortex (PMDr, PMDc, PMVr, and PMVc). Second, it has been used to refer specifically to the dorsal part of the lateral premotor cortex (PMDr and PMDc). Third, it has been used to refer to all cortical motor areas excluding the primary motor cortex. The looseness with which the term is used can lead to some confusion.

The term *motor cortex* originally referred to the lateral motor strip, when that area was believed to be the only motor map of the body. It is now used variously to indicate the primary motor cortex, the lateral motor strip including primary motor and lateral premotor cortex, all cortical motor areas inclusively, or whatever part of the cortical motor system is under discussion at the moment. Because one theme in this book is that the divisions among motor areas are not as clear as sometimes suggested, it is useful to have a term that is intentionally ambiguous.

Chapter 2

Early Experiments on Motor Cortex

INTRODUCTION

This chapter describes how the dominant ideas about motor cortex first emerged. Many of the forgotten initial observations are still of direct scientific relevance. Moreover, the history shows how myths and factoids evolved and became resistant to change. Tracing these scientific stories reminds us that the prevailing beliefs at any time are not to be trusted. Certain beliefs, such as the early view that the cortex is inexcitable, or the more recent view of a discrete somatotopic map of the body in the primary motor cortex, are repeated and simplified through repetition until they become parables of uncertain validity.

This chapter traces motor cortex research from its beginning to the motor maps of Penfield and Boldrey (1937) and Woolsey et al. (1952). This segment of the history is mainly about electrical stimulation applied to the surface of the cortex. Using this technique, researchers drew motor maps of greater and greater elaboration. After Penfield and Woolsey, more fine-grained techniques such as microstimulation and single-neuron recording were used to probe the details and, as might have been expected, reopened all the same questions and debates. The more modern story of motor cortex, post-1952, is summarized in Chapters 3 through 5.

SWEDENBORG

There is some variation of opinion about where to begin the history of motor cortex research. Gross (1997) describes the remarkable case of Emanuel Swedenborg, a Swedish philosopher and mystic of the eighteenth century. In 1744 Swedenborg wrote a treatise on the brain. He proposed, among other remarkably accurate hypotheses, that movement was controlled by the cerebral cortex; that the feet were controlled by the uppermost part of the cortex; that the midsection of the body including the abdomen was controlled by the midregion of the cortex; and that the face was controlled by the lowermost part of the cortex. At that time the prevailing view of the cerebral cortex was of a nutritive or protective rind that served no mental function (Gross, 1997), yet Swedenborg correctly described the functional importance of the cortex and the upside-down topography of the motor map. Unfortunately his writings do not describe how he deduced these properties of the cortex. He is known to have visited contemporary physiology labs and may have observed a set of suggestive experiments that were never independently published. In any case,