

Complex Movements Evoked by Microstimulation of Precentral Cortex

Michael S.A. Graziano,¹ Charlotte S.R. Taylor, and Tirin Moore

Department of Psychology
Princeton University
Princeton, New Jersey 08544

Summary

Electrical microstimulation was used to study primary motor and premotor cortex in monkeys. Each stimulation train was 500 ms in duration, approximating the time scale of normal reaching and grasping movements and the time scale of the neuronal activity that normally accompanies movement. This stimulation on a behaviorally relevant time scale evoked coordinated, complex postures that involved many joints. For example, stimulation of one site caused the mouth to open and also caused the hand to shape into a grip posture and move to the mouth. Stimulation of this site always drove the joints toward this final posture, regardless of the direction of movement required to reach the posture. Stimulation of other cortical sites evoked different postures. Postures that involved the arm were arranged across cortex to form a map of hand positions around the body. This stimulation-evoked map encompassed both primary motor and the adjacent premotor cortex. We suggest that these regions fit together into a single map of the workspace around the body.

Introduction

The primate brain is thought to contain a map of the body that is used to control movement. This map is stretched across the cortex in front of the central sulcus, with the feet at the top of the brain and the face near the bottom (e.g., Fritsch and Hitzig, 1870; Penfield and Boldrey, 1937; Woolsey et al., 1952; Strick and Preston, 1978; Huntley and Jones, 1991). Many fundamental questions about this map remain unanswered. First, the somatotopic organization within the precentral gyrus is in question. A well-defined map of muscles does not appear to exist. Different body parts are represented in an intermingled fashion (Penfield and Boldrey, 1937; Woolsey et al., 1952; Donoghue et al., 1992; Schieber and Hibbard, 1993; Sanes et al., 1995). Though it is possible to distinguish a broad leg area, arm area, and face area, there appears to be little somatotopic organization within each of these areas. The significance of this apparent disorder is not clear. Second, when neurons at one location in the map become active, do they specify joint angle, muscle tension, force, velocity, direction, or some other movement parameter? Though single neuron studies have addressed this issue, it is not yet resolved (e.g., Kakei et al., 1999; Moran and Schwartz, 2000; Scott, 2000; Todorov, 2000). Third, the relationship

between primary motor cortex and the adjacent premotor cortex is uncertain. A traditional view is that premotor cortex instructs primary motor cortex, which in turn instructs the spinal cord (Fulton, 1935). However, both premotor and primary motor cortex project directly to the spinal cord in complex, overlapping patterns (Dum and Strick, 1991, 1996; Maier et al., 2002), suggesting that a simple hierarchy may not be correct. To study these issues, we electrically stimulated sites within primary and premotor cortex and measured the resultant behavior.

Stimulation of the primate brain through microelectrodes has become a widely used technique to study the behavioral function of brain areas (Tehovnik, 1996). Microstimulation activates not only the neuronal elements near the electrode tip, but also a network of neurons sharing connections with those directly stimulated. Thus, the effect of electrical stimulation is thought to depend on the recruitment of physiologically relevant brain circuits. Stimulation has been used to uncover maps of eye movement in the frontal and supplementary eye fields, the lateral intraparietal area, and the superior colliculus (Robinson and Fuchs, 1969; Robinson, 1972; Schiller and Stryker, 1972; Bruce et al., 1985; Tehovnik and Lee, 1993; Thier and Andersen, 1998). In these areas, stimulation evokes saccadic eye movements that are similar or identical to those made voluntarily. These studies typically use stimulation trains on the same time scale as a normal saccade; shorter stimulation trains result in truncated movements (Stanford et al., 1996). In the superior colliculus, stimulation trains up to 400 ms in duration, on the same time scale as a normal head movement, evoke coordinated movements of the head and eyes (Freedman et al., 1996). In the smooth pursuit area in the arcuate sulcus, stimulation trains up to 500 ms in duration are used to evoke long, smooth pursuit movements of the eyes (Gottlieb et al., 1993).

Stimulation is also used in sensory areas to influence perceptual decisions. In primary somatosensory cortex, stimulation can mimic the effect of a tactile stimulus on the finger (Romo et al., 1998). In that experiment, the duration of the stimulation train was set to 500 ms, matching the duration of the externally applied tactile stimulus. In visual areas MT and MST, stimulation can influence the monkey's perceptual judgements (Salzman et al., 1990; Britten and VanWezel, 1998; DeAngelis et al., 1998). These studies used stimulation trains of 1000 ms, estimated to match the time scale of the monkey's perceptual decision.

Stimulation applied to the lateral hypothalamus of rats and primates evokes feeding behaviors, and stimulation applied to the posterior hypothalamus evokes mating behaviors (Caggiula and Hoebel, 1966; Hoebel, 1969; Quaade et al., 1974; Okada et al., 1991). When the stimulation train stops, the evoked behavior stops. These stimulation trains are typically 10–30 s long, and sometimes as long as 3 min, again roughly matching the time course of the behaviors under study.

Stimulation is thus used to study a range of brain areas, evoking meaningful, coordinated movements and

¹Correspondence: graziano@princeton.edu



Figure 1. An Example of a Complex Posture Evoked from Monkey 1 by Microstimulation of Precentral Cortex

When this site was stimulated the left hand closed into a grip posture, turned to the face, moved toward the mouth, and the mouth opened. Stimulation was for 500 ms at 100 μ A and 200 Hz. Drawings were traced from video footage acquired at 30 frames per second. The 11 dotted lines show the frame-by-frame position of the hand for 11 different stimulation trials. Each dot shows the part of the video image of the hand that was farthest from the elbow. The start point of each trajectory was distant from the mouth; the end point was at or near the mouth.

behavioral repertoires and influencing perceptual decisions. In most cases, the duration of the stimulation train is chosen to match the time course of the behavior being studied.

Electrical stimulation has also been used to investigate primary motor and premotor cortex. Most previous studies of motor and premotor cortex used short stimulation trains, usually less than 50 ms, that evoked brief muscle twitches (e.g., Asanuma et al., 1976; Strick and Preston, 1978; Sessle and Wiesendanger, 1982; Weinrich and Wise, 1982; Kurata, 1989; Sato and Tanji, 1989; Huntley and Jones, 1991; Preuss et al., 1996; Wu et al., 2000). The purpose of these previous studies was to map the location on the body affected by stimulation, rather than to study the evoked movement itself. In the present study, we applied stimulation trains of 500 ms, approximating the duration of a monkey's typical reach (e.g., Georgopoulos et al., 1986; Reina et al., 2001). We report that stimulation on this behaviorally relevant time scale allowed complex and coordinated movements to unfold.

Results

Complex Postures Evoked by Stimulation

The diagrams in Figure 1, traced from video footage, show the results of electrically stimulating one site in the precentral gyrus in the right hemisphere of monkey 1. When this site was stimulated with 100 microamps (μ A) for 500 ms, the left hand closed in a grip posture with the thumb against the forefinger, the forearm supinated such that the hand turned toward the face, the elbow and shoulder joints rotated to bring the hand smoothly to the mouth, and the mouth opened. This complex stimulation-induced movement occurred on every trial and began at a short latency after the stimulation (<33 ms, within one video frame).

Stimulation at this site did not specify a single direction of arm movement, but rather a final posture of arm, hand, and mouth. As shown in Figure 1, different directions of arm movement could be elicited depending on the starting position of the hand. When the stimulation was applied for 1000 ms, the monkey moved the hand to the mouth and then usually froze with the hand at the mouth and the mouth partially open until the end of the stimulation. Stimulation for 100 ms caused a truncated movement of the hand, arm and mouth that may

correspond to the previously reported muscle twitches. When an obstacle was placed between the hand and the mouth, the hand did not move around the obstacle during stimulation but hit it and was stopped.

Hand-to-mouth postures were evoked from 12 neighboring sites (eight electrode penetrations) in monkey 1. The location of these sites in the precentral gyrus is shown in Figure 7. A similar cluster of ten hand-to-mouth sites was found in monkey 2. In all cases, the movement appeared to be natural and coordinated. We never evoked a hand-to-mouth posture in which the hand faced away from the mouth, in which the arm was in a twisted or unnatural posture, or in which the mouth closed instead of opened.

Stimulation of other sites in the precentral gyrus evoked different postures. Figure 2A–2F shows the results from six example sites in monkey 2. In each case, stimulation caused the arm to move to a specific posture and thus the hand to converge toward a location in space. The stimulation-evoked postures were not limited to the hand and arm representation: Figure 2G shows the results from a site in the face and mouth representation. Stimulation at this site caused a consistent, short latency (<33 ms) movement of the mouth, lips, and tongue toward a specific posture. If the jaw was initially closed, stimulation caused it to open part way. If the jaw was initially wide open as in a threat display, stimulation caused it to close partially to the same posture. Likewise, regardless of the starting position of the tongue in the mouth, stimulation caused the tongue to move to the same final position, aimed toward the left canine. Starting postures for three example trials are shown; a similar final posture was obtained on all 72 trials tested.

Figure 3 shows the results for another example site. Stimulation at this site evoked a final posture of the arm and hand including a partial flexion of the elbow. When the arm was fully outstretched, stimulation caused the elbow to flex to its final posture. When the elbow was fully flexed, stimulation caused it to extend to the final posture. Were these different directions of motion initiated by activity in different muscles? That is, can stimulation of one site in cortex activate different muscles depending on the starting position of the arm? To answer this question, we probed the electromyographic (EMG) activity of upper arm muscles. Figure 3 shows the EMG activity evoked by a 100 ms stimulation train while the arm was relaxed and held in either an extended

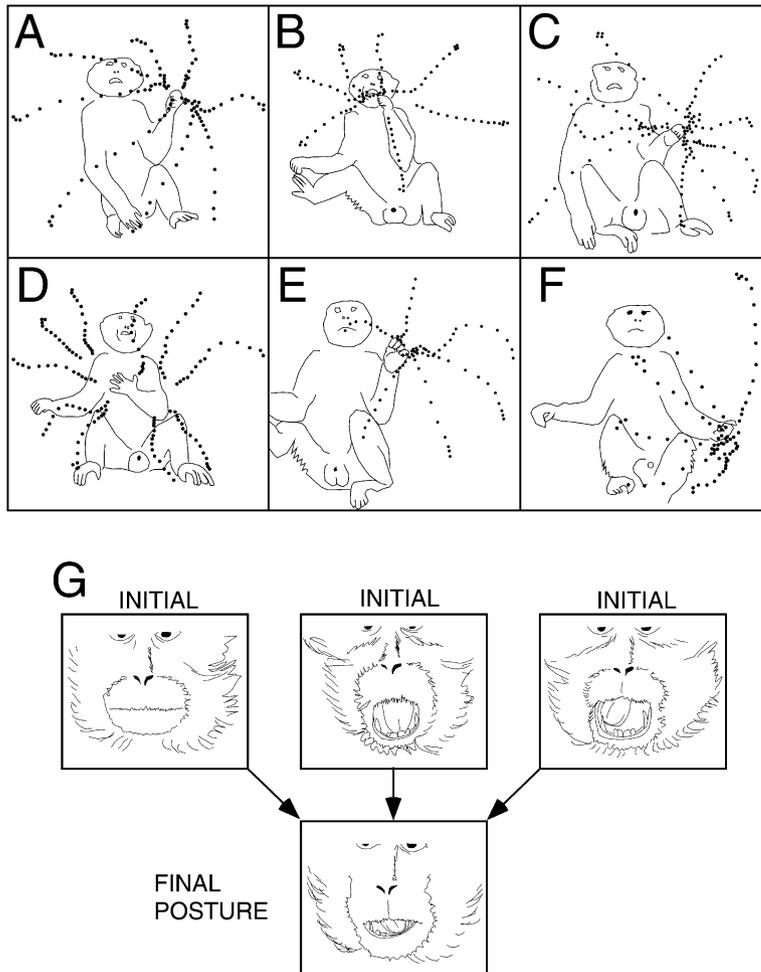


Figure 2. Examples of Postures Evoked by Microstimulation of Precentral Cortex

(A–F) Six examples of postures of the left arm evoked from monkey 2. Stimulation on the right side of the brain caused movements mainly of the left side of the body. Postures of the right limbs shown in these traced video frames are incidental and not dependent on the stimulation. Final postures that involved the left hand near the edge of the workspace, such as in (F), could not be tested from all directions, but still showed convergence from the range of initial positions tested.

(G) A posture of the mouth and tongue evoked from monkey 1. When this site was stimulated, the mouth opened partly and the tongue pointed toward the left canine (final posture). Three initial postures of the mouth and tongue are shown. For the evoked movements shown in (A), (D), and (E), stimulation was at $50 \mu\text{A}$; (B), (C), and (G), $100 \mu\text{A}$; (F), $75 \mu\text{A}$. For all sites, stimulation trains were presented for 500 ms at 200 Hz.

or a flexed posture. When the arm was fixed in a fully extended posture, stimulation evoked a burst of activity in the biceps and a small, significant drop in activity in the triceps. This pattern of muscle activity is appropriate for initiating a flexion of the elbow toward the final posture. When the arm was fixed in a fully flexed posture, stimulation evoked a burst of activity in the triceps and not the biceps. This pattern of activity is appropriate for initiating an extension of the elbow toward the final posture. Stimulation at this site therefore did not specify a fixed set of muscle activations. Instead, the mapping from cortex to muscles depended on arm position in a way that was consistent with specifying a final posture.

For most sites (279/324, 86%) tested in the precentral gyrus and the anterior bank of the central sulcus, stimulation evoked a repeatable final posture of some part or parts of the body. For the remaining sites, the movements were more difficult to interpret, for the following reasons. To demonstrate a final posture, it was necessary to start the relevant body part at different positions and then to confirm that the body part moved convergently toward one final position. This assessment was often impossible for sites in the face representation, for which the facial muscles contracted. These evoked movements may have corresponded to meaningful facial expressions, but we did not classify them as pos-

tures. Also, at some sites, the evoked movement was weak, and thus no final posture could be convincingly demonstrated. Stimulation of eight sites anterior to the arcuate sulcus, presumably in the frontal eye fields, evoked saccadic eye movements but not limb postures. Stimulation of nine sites posterior to the central sulcus, presumably in primary somatosensory cortex, evoked occasional finger movements but not limb postures.

Comparison of Evoked Movements to Spontaneous Movements

Stimulation-evoked movements of the hand were generally smooth and matched the bell-shaped velocity profile of a normal reach (Bizzi and Mussa-Ivaldi, 1989). An analysis of one example site is shown in Figure 4. Stimulation at this site caused the hand to move to the mouth. The start of each hand trajectory was not analyzed, because the voluntary movement of the arm preceding the stimulation may have influenced the beginning of the stimulation-evoked movement. Figure 4A shows the average of 12 stimulation trials, aligned on the end of the movement. The smooth increase and then decrease in velocity as the hand approached the mouth is characteristic of a skilled reach (Morasso, 1981). Figure 4B shows the average of 20 spontaneous movements of the hand to the mouth, such as when the monkey

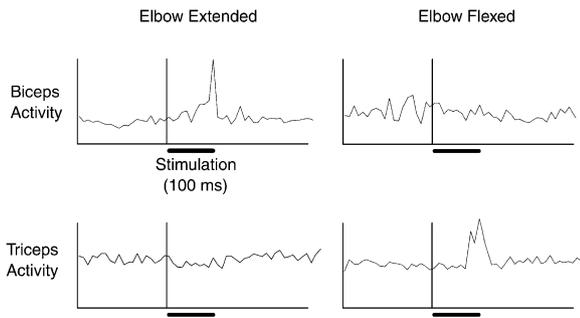


Figure 3. Electromyographic (EMG) Activity from Muscles of the Upper Arm during Stimulation of One Site in Primary Motor Cortex. Stimulation at this site for 500 ms at 100 μ A evoked a final posture of the arm and hand including a partial flexion of the elbow. When the elbow was fully extended, stimulation caused it to flex to its final posture. When the elbow was fully flexed, stimulation caused it to extend to the final posture. The site was then tested by fixing the arm in an extended or a flexed position, applying a 100 ms stimulation train, and measuring EMG activity from the biceps and triceps lateralis muscles. For each condition, a paired t test was used to compare the prestimulation activity (in the 200 ms period immediately preceding stimulation) to the activity during and just after stimulation (in the 150 ms period starting at stimulation onset). For Biceps and Elbow Extended, the evoked activity during and just after stimulation was significantly above the prestimulation activity (14 trials, $t = 4.41$, $p = 0.001$). For Biceps and Elbow Flexed, the activity during and after stimulation was not significantly different from the prestimulation activity (14 trials, $t = 0.254$, $p = 0.804$). For Triceps and Elbow Extended, the activity during and after stimulation was significantly below the prestimulation activity; that is, the muscle became more relaxed (14 trials, $t = 2.68$, $p = 0.019$). For Triceps and Elbow Flexed, the activity during and after stimulation was significantly above the prestimulation activity (14 trials, $t = 2.82$, $p = 0.015$).

brought food to the mouth. The velocity profile of these spontaneous movements was similar to that of the stimulation-evoked movements.

Although the stimulation-evoked movements were similar to the monkey's spontaneous movements, they were not simply spontaneous movements that happened to occur around the time of the stimulation. The evoked movements could be distinguished from spontaneous movements in the following ways.

First, the evoked movements occurred consistently at a short latency after the stimulation (<66 ms, or within two video frames, for most sites). These short latencies match those reported previously (e.g., Donoghue et al., 1992).

Second, the evoked movements were often in opposition to the expected natural movements of the monkey. If the monkey was actively reaching toward a fruit reward, stimulation would cause the monkey to abort its reach and bring the hand to the evoked posture; when the stimulation ended, the monkey's arm was released from the posture, and he would reach again for the fruit reward. If the fruit was already in the monkey's hand, normally he would put it immediately in his mouth; if stimulated, however, he would first move the hand to the evoked posture; when the stimulation was ended, the monkey would then put the fruit in his mouth. During stimulation, when an obstacle was placed between the hand and the final position, the hand did not move

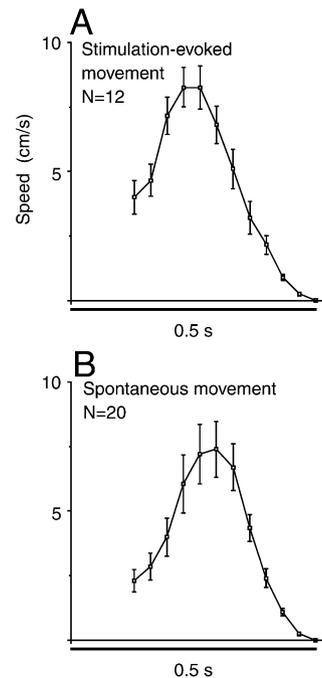


Figure 4. Velocity Profile of the Hand as It Approached the Mouth (A) Stimulation-evoked movements of the hand to the mouth. Mean of 12 trials. Error bars are standard error. Trials were aligned on the end of the movement when the hand stopped near the mouth. The beginning of the movement was not analyzed to avoid contamination by the voluntary movement of the limb before the start of stimulation. (B) Velocity profile for spontaneous movements of the hand to the mouth, showing that spontaneous movements followed the same pattern as stimulation-evoked movements.

around the obstacle in a goal-directed fashion but instead was stopped and remained pressing against the obstacle until the end of the stimulation.

Finally, six sites were tested before and during anesthesia (see Experimental Procedures). We used a mixture of ketamine (10 mg/kg) and acepromazine (0.1 mg/kg) injected IM. For three of the sites, we also added IV sodium pentobarbital (2 mg/kg). After the monkey became anesthetized, the complex stimulation-evoked movement could still be obtained, although the movement was always weaker and less consistent. For the two hand-to-mouth sites that were tested in this fashion (one tested with ketamine and acepromazine, the other tested also with sodium pentobarbital), all components of the movement were observed under anesthesia: the shaping of the hand into a grip posture, the movement of the arm toward the mouth, and the opening of the mouth.

A Map of Hand Locations

Within the large arm and hand representation, the stimulation-evoked postures were organized across the cortex to form a map of hand positions in space. Eight example postures from different locations in the map are shown in Figure 5. An especially complex posture is shown in Figure 5C. The monkey turned its hips toward the left and appeared to reach with the left hand and foot toward a common location in lower space.

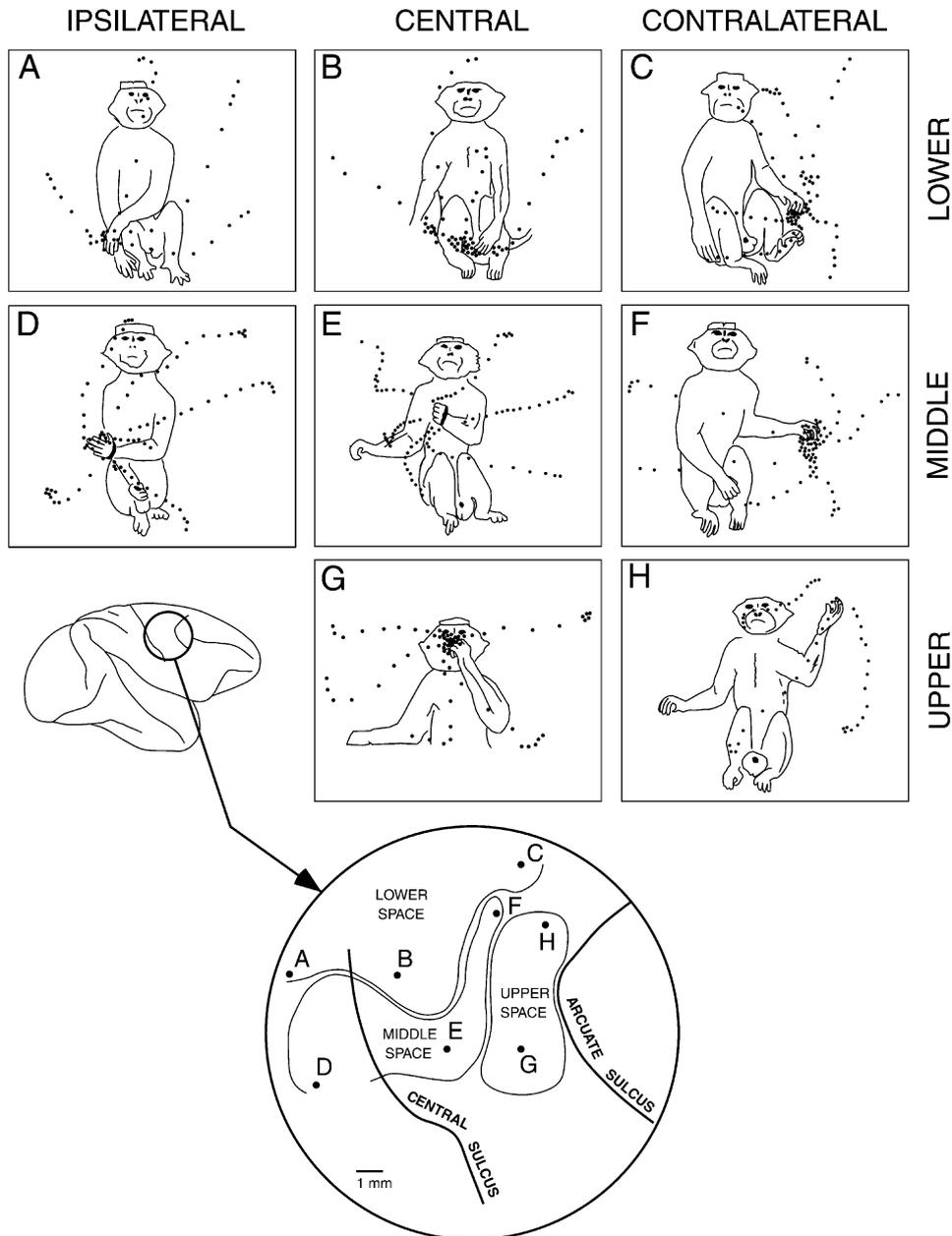


Figure 5. Eight Example Postures Illustrating the Topographic Map Found in Precentral Cortex of Monkey 1

A similar map (not shown) was obtained in monkey 2. The circle on the brain shows the area that could be reached with the electrode. The magnified view at the bottom shows the locations of the stimulation sites. The area to the left of the lip of the central sulcus represents the anterior bank of the sulcus. Stimulation on the right side of the brain caused movements mainly of the left side of the body. Postures of the right arm shown in these traced video frames are incidental and not dependant on the stimulation. For the evoked movements shown in (A) and (G), stimulation was at 50 μ A. In (B)–(F) and (H), stimulation was at 100 μ A. For all sites, stimulation trains were presented for 500 ms at 200 Hz.

A more detailed summary of the map is shown in Figure 6. Ventral and anterior sites corresponded to hand positions in upper space, while dorsal and posterior sites corresponded to hand positions in lower space (Figure 6A). Along a roughly orthogonal axis in the map, the hand position varied from the far contralateral side of the body to positions ipsilateral to the body midline (Figure 6B). The distance of the hand from the body did not appear to be mapped across cortex in a systematic

fashion. One unexpected property of the map of arm postures is that it encompassed both primary motor cortex and the adjacent premotor cortex. (For criteria used to distinguish primary motor from premotor cortex, see Experimental Procedures.) Primary motor cortex corresponded mainly to the representation of the central space directly in front of the monkey's chest.

The map of hand locations, which occupied the hand and arm representation in motor and premotor cortex,

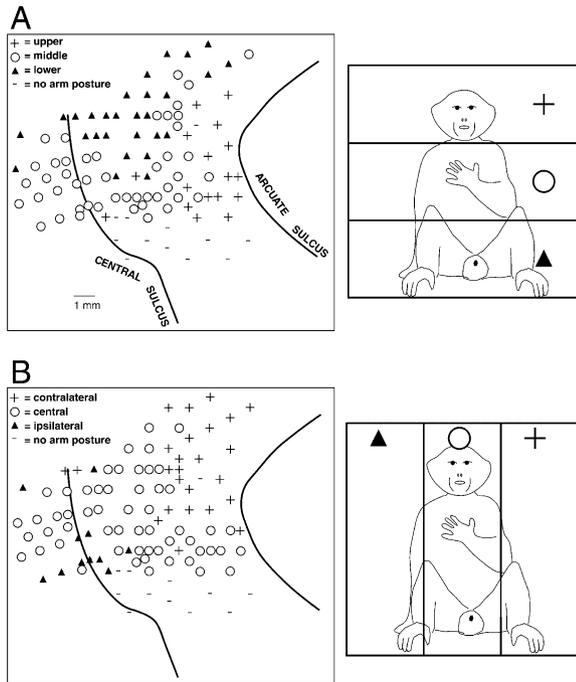


Figure 6. Topography of Hand and Arm Postures in the Precentral Gyrus Based on 201 Stimulation Sites in Monkey 1

A similar map (not shown) was found in monkey 2. Most points represent two to three sites tested at different depths. Sites plotted to the left of the line labeled Central Sulcus were located in the anterior bank of the sulcus.

(A) Distribution of hand positions along the vertical axis, in upper, middle, and lower space. Each site was categorized based on the center of the range of evoked final positions. Height categories were defined as follows: lower = 0 to 12 cm from bottom of monkey, middle = 12 to 24 cm, upper = 24 to 36 cm. Dashes show electrode penetrations where no arm postures were found; usually the postures from these locations involved the mouth or face.

(B) Distribution of hand positions along the horizontal axis, in contralateral, central, or ipsilateral space. Horizontal categories were defined as follows: contralateral = 6 to 18 cm contralateral to midline, central = within 6 cm of midline (central 12 cm of space), ipsilateral = 6 to 18 cm ipsilateral to midline.

was embedded in a larger, rough map of the monkey's body. At more ventral sites, the mouth was recruited. At more dorsal sites, the leg and foot were recruited. We obtained this same rough map of body parts whether we used short (100 ms) stimulation to evoke muscle twitches or longer (500 ms) stimulation to evoke coordinated movements. That is, in both cases, the same body parts were affected. The somatotopy that we found matches the previously reported, crude somatotopy in the precentral gyrus (e.g., Penfield and Boldrey, 1937; Woolsey et al., 1952; Lemon and Porter, 1976; Fetz et al., 1980; Donoghue et al., 1992; Schieber and Hibbard, 1993; Sanes et al., 1995).

Specialized Subregions Related to Finger Movement

The open circles in Figure 7 show sites where hand-to-mouth movements were evoked. The hand-to-mouth sites always involved a grip posture of the fingers. These sites, clustered just posterior and ventral to the bend in

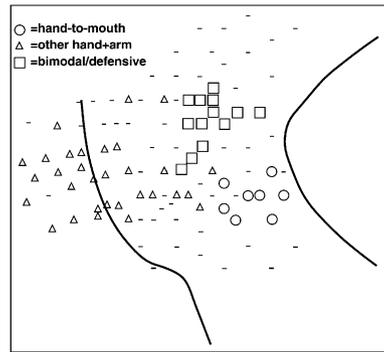


Figure 7. Specialized Subregions within the Map of Stimulation-Evoked Postures Based on Data from Monkey 1

Circles show hand-to-mouth sites; these always involved a grip posture of the hand in addition to a movement of the arm that brought the hand to the mouth. Triangles show other sites where stimulation evoked both a hand and an arm posture; these sites often involved the hand moving into central space and the fingers shaping into a specific configuration. Squares show sites where bimodal, visual-tactile responses were found and stimulation evoked defensive movements.

the arcuate sulcus, corresponded roughly to an area of premotor cortex thought to control grip (Rizzolatti et al., 1988). One possible reason why this area of cortex emphasizes prehension is that it may represent a special region of the workspace near the mouth, in which monkeys often use their fingers to grip food.

The open triangles in Figure 7 show other sites from which finger movements were evoked. That is, stimulation at these sites evoked not only specific hand locations in space but also a variety of hand postures. These hand postures included a grip with the thumb against the forefinger, a fist (e.g., Figure 5E), an open hand with all five digits splayed (e.g., Figure 2D), rotations of the wrist, and also a pronation or supination of the forearm. We found that the current threshold for evoking a twitch was especially low at these sites, typically less than 12 μ A. The low threshold in this part of the map appears to reflect the emphasis on finger and wrist movements, which generally required less current to evoke than arm movements. This subregion of the map roughly corresponds to the primary motor representation of the hand. One possible reason for the emphasis on finger, wrist, and forearm movements within this part of the map is that it represents the space directly in front of the chest where monkeys tend to manipulate objects with their hands.

Defensive Movements Evoked from Bimodal Sites

In addition to its motor output, the precentral gyrus also receives sensory input presumably for the guidance of movement. One class of precentral neuron has a distinctive type of response to tactile and visual stimuli (Rizzolatti et al., 1981; Fogassi et al., 1996; Graziano et al., 1997). These bimodal neurons typically have a tactile receptive field on the face, arms, or torso and a visual receptive field adjacent to the tactile receptive field, extending about 20 cm into the space surrounding the body. A smaller proportion of these cells also respond to auditory stimuli presented in the space near the tactile

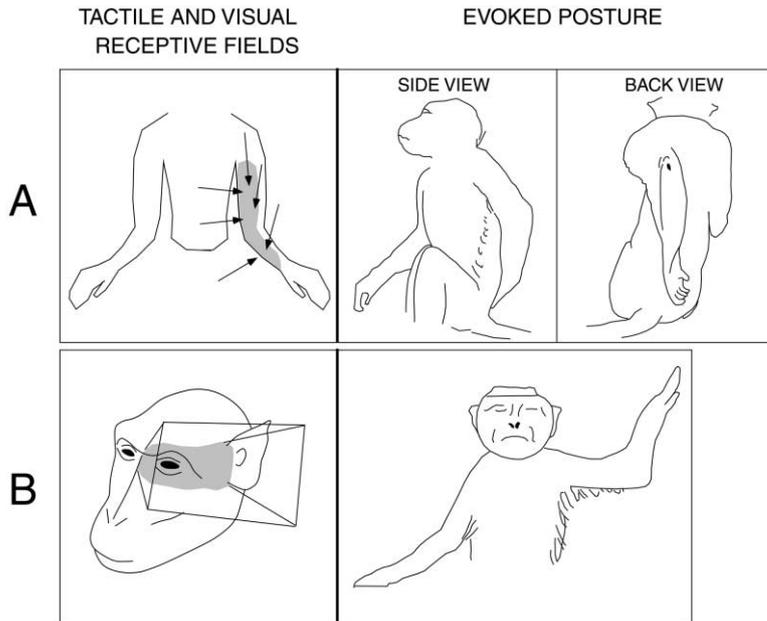


Figure 8. Sensory-Motor Integration in Precentral Cortex

(A) Neurons at this site responded to a touch on the arm (within the shaded area) and to nearby visual stimuli moving toward the arm (indicated by arrows). Microstimulation caused the arm to move to a posture behind the back. Stimulation for 500 ms, 200 Hz, and 50 μ A. (B) Multineuron activity at this site responded to a touch on the contralateral upper part of the face and to visual stimuli in the space near this tactile receptive field. Microstimulation evoked a complex defensive posture involving a facial squint, a head turn, and the arm and hand moving to a guarding position. Stimulation for 500 ms, 200 Hz, and 50 μ A.

receptive field (Graziano et al., 1999). These cells are usually clustered just posterior to the bend in the arcuate sulcus (Graziano and Gandhi, 2000). Although their sensory properties were extensively characterized, their function was unknown.

In monkey 1, bimodal, visual-tactile neurons were found at 27 sites (13 electrode penetrations) clustered behind the bend in the arcuate sulcus, as shown by the open squares in Figure 7. A similar bimodal zone was found in the second monkey. The results from stimulating one example site in this bimodal zone are shown in Figure 8A. Before electrical stimulation, we studied single neurons and multineuron activity at this site. When the eyes were covered, the neurons responded to touch on the left arm. When the eyes were uncovered, the neurons also responded to the sight of objects near and approaching the arm. When this cortical site was electrically stimulated, the arm moved rapidly to a posture behind the monkey's back. This pairing of a response to nearby objects approaching the arm with a motor output that withdraws the arm suggests that these neurons help to guard the arm from an impending threat. Regardless of the initial position of the arm, stimulation always evoked this final "guarding" posture.

A second example is shown in Figure 8B. When the eyes were covered, the neurons at this site responded to touching the left temple. When the eyes were open, the neurons responded to the sight of objects in the space near the temple. Electrical stimulation of this site caused the left eye to close entirely, the right eye to close partially, the face to contract into a grimace, the head to turn toward the right, the left arm to extend rapidly into the upper left space, and the left hand to turn such that the palm faced outward. (For these tests, the head bolt was loosened, allowing the head to turn to the right or left.) That is, stimulation caused the monkey to mimic the actions of flinching from an object near the side of the head and thrusting out a hand to fend off the object.

At another bimodal site, the neurons responded to a touch on the forehead and to the sight of objects approaching the forehead. Stimulation of that site caused the eyes to close and the head to pull downward. At yet another site, the neurons responded to touching the back of the arm near the elbow and to the sight of objects moving in the periphery near the arm. Stimulation caused the elbow to pull rapidly forward and inward toward the midline.

Does the electrical stimulation cause a sensory percept such as pain on a part of the body, causing the monkey to flinch in reaction to that sensation? Although this is possible, we suggest that it is probably not the case. Instead, we suggest that the stimulation evokes a specific motor plan devoid of any sensory component or emotional valence. Three observations support this view. First, the evoked movement occurs at a latency of less than 33 ms, probably too short a time for the monkey to respond to a sensory percept. Second, after each stimulation, as soon as the stimulation train ended, the monkey returned to a normal resting posture or to feeding itself pieces of fruit. In contrast, when the monkeys were made to flinch by presenting threatening stimuli to the side of the face, we found that they did not return to a quiet resting posture after the sensory stimulus was removed. Instead, they behaved in an agitated fashion and continued to defend the threatened part of the body. Third, we found that the same defensive movements could be elicited from an anesthetized monkey that did not react to any sensory stimuli (see Experimental Procedures). Taken together, these findings suggest that the stimulation-induced defensive movements do not operate indirectly by way of a sensory percept, but instead directly activate a motor output.

Bimodal, visual-tactile responses were found at 50 sites in the two monkeys. For all of these sites, the evoked postures were consistent with flinching, avoiding, or defending against an object located in the bimodal receptive field. The bimodal sites therefore may be part

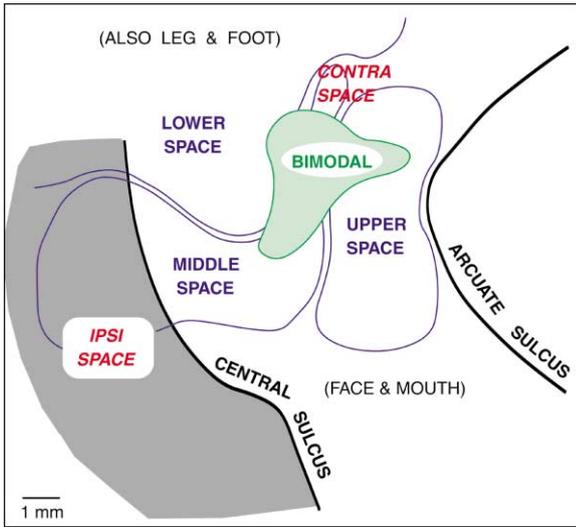


Figure 9. The Organization the Precentral Gyrus as Determined by Microstimulation on a Behaviorally Relevant Time Scale

Blue lines show vertical axis of hand position map indicated by Upper Space, Middle Space, and Lower Space. Red shows horizontal axis of hand position map indicated by Contra Space and Ipsi Space. Green shows bimodal, visual-tactile zone from which defensive postures were evoked. Shaded area to the left of the lip of the central sulcus represents the anterior bank of the sulcus.

of a specialized sensory-motor pathway that detects and locates threatening objects near the body and specifies the appropriate postures to defend the body. The bimodal neurons may have other functions as well, but defense of the body appears to be a major function.

Discussion

Figure 9 shows a summary of the results. Stimulation for 500 ms at each site in cortex evoked a specific posture of one or more body parts. Postures of the arm and hand were arranged across cortex to form a map of spatial locations to which the hand moved. This map of stimulation-evoked postures extended from the anterior bank of the central sulcus to the lip of the arcuate sulcus, encompassing both primary motor and the adjacent premotor cortex. A bimodal zone, from which defensive movements were evoked, was located in the middle of the map.

Does this stimulation-evoked map reflect the normal function of the precentral gyrus? Stimulation of cortex is nonphysiological, and thus the results should be taken cautiously. Several aspects of the results, however, suggest that the stimulation-evoked movements may mimic normal ones. First, many of the evoked movements are highly coordinated across multiple joints. For example, the hand-to-mouth sites involve the fingers closing into a grip posture, the wrist and forearm rotating to orient the hand toward the face, the elbow and shoulder joints rotating to bring the hand to the mouth, and the mouth opening. Another example of complex coordination across many joints is provided by the defensive postures, in which the eye closes, the face contracts into a grimace, the head turns away, the arm moves to the

side, and the hand turns outward. This degree of coordination across so many joints, to produce a behaviorally meaningful movement, is unlikely to occur by chance coactivation of muscles.

Second, the movement of the hand appears to follow the distinctive velocity profile of a normal reach. This smooth velocity profile through space is thought to result from a complex coordination of timing and force across different joints (Morasso, 1981; Bizzi and Mussa-Ivaldi, 1989).

Third, stimulation evokes a systematic map of hand position across cortex. This map is difficult to explain by an abnormal scrambling of neuronal signals. Instead it suggests that the stimulation technique, just as in the oculomotor, visual, and somatosensory systems, has uncovered a meaningful, functional organization. We interpret these results cautiously, however. Each site in cortex may ultimately influence a range of movements, and electrical stimulation might evoke only the most strongly represented movement.

The map of postures reported here appears, at first, to contradict previous work on motor and premotor cortex. We suggest, however, that the present results do not contradict but rather extend previous findings in the following ways.

Muscle Twitches versus Complex Movements

We were able to replicate the common finding that brief stimulation trains evoke muscle twitches. Complex and coordinated movements unfolded only with stimulation trains on a behaviorally relevant time scale. For some sites, we also varied other stimulation parameters, such as the frequency (between 50 and 400 Hz), the current amplitude (between 25 and 150 μA), and the type of pulse (biphasic versus cathodal) and found similar results. The duration of the stimulation train appeared to be the critical factor distinguishing a complete, coordinated movement from a truncated movement or twitch. The threshold for producing a movement was statistically indistinguishable between 100 ms and 500 ms stimulation trains, suggesting that longer stimulation does not increase the probability of a movement but instead simply causes the stimulation-induced movement to continue for a longer period of time. (For 100 ms trains, mean threshold = 24.25 μA , SD = 18.32; for 500 ms trains, mean = 22.34 μA , SD = 15.81; $t = 0.66$, $p = 0.51$, $df = 140$.)

The 500 ms stimulation trains that we used match the duration of a monkey's typical reach (e.g., Georgopoulos et al., 1986; Reina et al., 2001). They also match the activity of a typical motor cortex neuron during movement. Neurons in motor cortex begin to respond before a reach and continue to fire at an elevated rate during the reach. The duration of this neuronal response is usually on a time scale of about 500 ms (e.g., Georgopoulos et al., 1986). One possible reason why the traditionally used stimulation trains of less than 50 ms evoke twitches rather than coherent movements is that the time course of those stimulation trains is an order of magnitude shorter than the time course of the neuronal activity that normally controls reaching.

Complex movement evoked by stimulation of motor cortex has been reported before, though not systemati-

cally studied. For example, Ferrier (1873) found that long electrical stimulation of motor cortex evoked coordinated, apparently "purposive" movements, unlike Fritsch and Hitzig (1870) who evoked only twitches using a brief electrical pulse.

The Topographic Organization of Motor Cortex

The present stimulation results are consistent with the standard somatotopic map in motor cortex, in which the feet are represented dorsally and the face and mouth are represented ventrally. This body map is known to be coarse. Different muscles are represented at the same location in cortex, and different locations in cortex represent the same muscle group. For example, previous studies found little organization within the large arm and hand representation (Penfield and Boldrey, 1937; Woolsey et al., 1952; Lemon and Porter, 1976; Fetz et al., 1980; Donoghue et al., 1992; Schieber and Hibbard, 1993; Sanes et al., 1995). One reason for this apparent disorganization may be that muscles from many parts of the body are employed in making a movement to one location in space. According to the present data, the parameter that varies across this map is not the location on the body where the muscles are activated, but rather the location near the body to which the movement is directed. Individual neurons in motor cortex are known to be broadly tuned for direction of movement, muscle force, and other parameters (e.g., Georgopoulos et al., 1986; Schieber and Hibbard, 1993; Kakei et al., 1999; Moran and Schwartz, 2000; Scott, 2000); one possibility is that a coherent posture is produced by the activation of a local population of these broadly tuned neurons.

The map of arm postures found in the present study is similar to the map of orbital eye position reported in the dorsomedial frontal cortex of monkeys (Tehovnik, 1995). In that study, electrical stimulation elicited eye movements that converged from different starting positions to a single final position. Different final positions were evoked from different cortical sites and were arranged topographically across the dorsomedial frontal cortex. (For a competing view of this oculomotor area, see Russo and Bruce, 2000.) The present results are also similar to the map of leg position found by electrical stimulation in the spinal cord of the frog (Giszter et al., 1993). In that study, stimulation elicited leg movements in which the foot converged from different starting positions to a single final position.

Primary Motor and Premotor Cortex: Distinct Parts to a Larger Map?

One of the most unexpected aspects of the present data is the finding of a single map that encompasses the precentral gyrus. This region of cortex is generally thought to consist of many distinct subregions, including primary motor cortex and several subdivisions of premotor cortex. Clearly these separate subregions exist, but our results suggest that they also fit together into the larger context of a single map. Different parts of the workspace have different behavioral requirements, and therefore the map of the workspace is not homogeneous. We found a low-threshold subregion that emphasizes manual dexterity in the central space in front of the chest. This region appears to correspond to the

primary motor hand representation. We found a hand-to-mouth subregion that emphasizes grip postures of the fingers near the mouth; this region appears to correspond to the premotor grasp region. Finally, we found a bimodal zone from which defensive postures were evoked; this zone appears to correspond to the premotor polysensory zone. Rather than viewing these as separate motor areas, we suggest that they are specializations within a larger map of the space around the monkey's body.

Many maps in the brain contain specialized subregions that have distinct properties. For example, in primary visual cortex, the foveal representation is different from the peripheral representation in physiological properties and even in anatomical connections (e.g., Kennedy et al., 1986; Colby et al., 1988). A naive investigator might conclude that the foveal representation is a separate visual area at a more primary level in a hierarchy, processing details at a finer grain. Yet the two parts of primary visual cortex are joined together by a single topographic map. In the same fashion, on the basis of the present data, we propose that primary motor cortex and the adjacent premotor cortex may be different from each other and yet fit together into a single map of complex postures.

Experimental Procedures

In total, 201 cortical sites were studied in 98 electrode penetrations in the right hemisphere of monkey 1, and 140 sites were studied in 92 electrode penetrations in the right hemisphere of monkey 2. Sites were studied in the following fashion. The monkey sat in a primate chair with the head fixed by a head bolt and the limbs and torso free. A hydraulic microdrive was used to lower a tungsten microelectrode (0.1–1.5 M Ω) into the cortex. For most electrode penetrations, we tested one to three depths separated by 0.5 or 1.0 mm. To study the anterior bank of the central sulcus, we tested at regular intervals of 0.5 or 1.0 mm until the electrode reached white matter and neurons could no longer be found. At each site, multineuron activity was studied during presentation of tactile and visual stimuli. Tactile stimuli included stroking of the skin and passive manipulation of the joints, and visual stimuli consisted of objects on the end of a wand. Neuronal responses during reaching and grasping movements were also qualitatively assessed. After neuronal responses were assessed, electrical stimulation was applied by means of a Grass stimulator (S88) and two stimulus isolation units (SIU6). The ground lead for the stimulation was in contact with the saline covering the exposed dura and surrounding bone within the recording chamber. Stimulation was triggered by a handheld button and consisted of a train of biphasic pulses: each pulse had a negative followed by a positive phase, each phase 0.2 ms in duration. At most sites, the pulses were presented at 200 Hz. At some sites, we tested rates between 50 and 400 Hz and found similar postures. At a few sites, we also tested with cathodal pulses instead of biphasic pulses and always obtained the same result. For threshold measurements, the current was varied between 0 and 100 μ A to determine the lowest current that evoked a movement at least 50% of the time. To study the evoked movement, the current was usually set between 25 and 150 μ A. Current was measured via the voltage drop across a 1 k Ω resistor in series with the return lead of the stimulus isolation units. The duration of each train was usually set to 500 ms. At many sites, we also tested with train durations of 100 ms and 1000 ms.

In order to study the effect of different starting postures, stimulation was applied while the monkey performed a simple reaching task. A small piece of fruit was placed at one of many possible locations around the monkey, and the monkey reached for the fruit. On about half of the trials, stimulation was applied as the hand reached the target location but before the monkey had grasped the

fruit. Stimulation was also applied during the monkey's spontaneous movements and while the monkey was sitting quietly with the arm stationary. Data were collected by videotaping the monkey's movements from a standard front and side view and simultaneously recording the time of stimulation. Movements were reconstructed off line from individual video frames. Because of the complexity of the movements and the involvement of all parts of the body (fingers, tongue, trunk, etc.), other types of data collection such as tracking the position of a few lights on the arm were inadequate.

For some cortical sites, the velocity of evoked hand movement was measured by recording the movement on film with the camera angle normal to the plane in which the hand moved. The position of the hand was then plotted frame by frame and measured. Velocity was determined by dividing the distance travelled by the time between frames (33 ms).

For some sites, EMG activity was measured from the biceps and triceps muscles. Fine insulated stainless steel wires were threaded into a 22 gauge syringe needle and inserted into the muscle. The wires had an exposed tip of 1–2 mm. Three wires were inserted to provide input to a differential amplifier and its ground (A-M Systems single neuron amplifier model 1800). Spacing between wires was approximately 0.5 cm. To measure EMG activity during a train of stimulation pulses delivered to the brain, the time of each stimulation pulse was measured and the EMG signal was sampled once within each 5 ms interpulse interval. The EMG was thus measured at a rate of 200 Hz. We confirmed that with this method the EMG measurement was free of any artifact from the electrical stimulation. It was then rectified and integrated.

For six sites including three bimodal sites, two hand-to-mouth sites, and one hand-to-central-space site, after testing the effect of stimulation in the awake preparation, we injected the monkey with an anesthetic and waited until the animal was unresponsive. We used a mixture of ketamine (10 mg/kg) and acepromazine (0.1 mg/kg) injected IM; for one bimodal site, one hand-to-mouth site, and the hand-to-central space site, we also added IV sodium pentobarbital (2 mg/kg). To test if the monkey could react to externally applied stimuli, we touched the monkey, manipulated the limbs, blew on the face, and finally pricked the eyelid with a needle. None of these stimuli elicited any response from the anesthetized monkey. Electrical stimulation, however, elicited the same movement components seen in the awake condition. The movements were generally weaker and less consistent under anesthesia.

Three lines of evidence suggest that the electrical stimulation did not damage the brain. (1) The evoked movements remained undiminished after hundreds of stimulation trials. (2) Immediately after stimulating, we could still record from single neurons, the neurons showed no abnormalities in their spike trains, and the neurons were still responsive. (3) The brain of monkey 1 was sectioned parasagittally at 50 μm on a freezing microtome and stained with cresyl violet. The tissue showed no sign of damage or gliosis at the sites of electrical stimulation. In contrast, at the sites of marking lesions, damage was clearly observable. The marking lesions were made in the week before sacrificing the monkey by passing a current of 20 μA DC through the electrode for 30 s.

Three criteria were used to localize primary motor and premotor cortex, though a sharp border between them was not observed.

- (1) *Cytoarchitecture*. On histological processing of the brain of monkey 1, we found that giant pyramidal cells in layer V were especially dense in the anterior bank of the central sulcus and in the adjacent cortex extending about 3 mm anterior to the sulcus. This area, Brodmann's area 4, is usually taken to be primary motor cortex (Evarts, 1981). Giant pyramidal cells were less dense in the more anterior cortex, presumably area 6 or premotor cortex.
- (2) *Current thresholds*. We determined the lowest current that could elicit an observable muscle twitch on half the trials. Thresholds were low in primary motor cortex (2–12 μA) and higher in premotor cortex (18–100 μA).
- (3) *Sensory responses*. Small tactile receptive fields on the hands or individual fingers, combined with responses to passive rotation of individual finger joints, were common in primary motor cortex, especially in the anterior bank of the central sulcus. Tactile receptive fields in premotor cortex were usually larger, for example including the hand and arm.

According to these criteria, primary motor cortex occupied the anterior bank of the central sulcus and extended several millimeters onto the gyral surface. Premotor cortex occupied the space between primary motor cortex and the arcuate sulcus.

Acknowledgments

We thank Charles Gross for his invaluable help. This work was supported by NIH grants EY-11347 and MH-12336 and Burroughs Wellcome grant #992817.

Received: December 10, 2001

Revised: April 3, 2002

References

- Asanuma, H., Arnold, A., and Zarzecki, P. (1976). Further study on the excitation of pyramidal tract cells by intracortical microstimulation. *Exp. Brain Res.* 26, 443–461.
- Bizzi, E., and Mussa-Ivaldi, F.A. (1989). *Motor Control: Handbook of Neuropsychology*, Volume 2, F. Boller and J. Grafman, eds. (New York: Elsevier Science Publishers), 229–244.
- Britten, K.H., and van Wezel, R.J. (1998). Electrical microstimulation of cortical area MST biases heading perception in monkeys. *Nat. Neurosci.* 1, 59–63.
- Bruce, C.J., Goldberg, M.E., Bushnell, M.C., and Stanton, G.B. (1985). Primate frontal eye fields. II. Physiological and anatomical correlates of electrically evoked eye movements. *J. Neurophysiol.* 54, 714–734.
- Caggiula, A.R., and Hoebel, B.G. (1966). Copulation reward site" in the posterior hypothalamus. *Science* 153, 1284–1285.
- Colby, C.L., Gattass, R., Olson, C.R., and Gross, C.G. (1988). Topographical organization of cortical afferents to extrastriate visual area PO in the macaque: a dual tracer study. *J. Comp. Neurol.* 269, 392–413.
- DeAngelis, G.C., Cumming, B.G., and Newsome, W.T. (1998). Cortical area MT and the perception of stereoscopic depth. *Nature* 394, 677–680.
- Donoghue, J.P., LeiBovic, S., and Sanes, J.N. (1992). Organization of the forelimb area in squirrel monkey motor cortex: representation of digit, wrist, and elbow muscles. *Exp. Brain Res.* 89, 1–19.
- Dum, R.P., and Strick, P.L. (1991). The origin of corticospinal projections from the premotor areas in the frontal lobe. *J. Neurosci.* 11, 667–689.
- Dum, R.P., and Strick, P.L. (1996). Spinal cord terminations of the medial wall motor areas in macaque monkeys. *J. Neurosci.* 16, 6513–6525.
- Evarts, E. (1981). Role of motor cortex in voluntary movements in primates. In *Handbook of Physiology, Section 1, The Nervous System, Volume II, Motor Control*, V.B. Brooks, ed. (Bethesda, MD: American Physiological Society), pp. 1083–1120.
- Ferrier, D. (1873). Experimental researches in cerebral physiology and pathology. *West Riding Lunatic Asylum Med. Rep.* 3, 30–96.
- Fetz, E.E., Finocchio, D.V., Baker, M.A., and Soso, M.J. (1980). Sensory and motor responses of precentral cortex cells during compatible passive and active joint movements. *J. Neurophysiol.* 43, 1070–1089.
- Fogassi, L., Gallese, V., Fadiga, L., Luppino, G., Matelli, M., and Rizzolatti, G. (1996). Coding of peripersonal space in inferior premotor cortex (area F4). *J. Neurophysiol.* 76, 141–157.
- Freedman, E.G., Stanford, T.R., and Sparks, D.L. (1996). Combined eye-head gaze shifts produced by electrical stimulation of the superior colliculus in rhesus monkeys. *J. Neurophysiol.* 76, 927–952.
- Fritsch, G., and Hitzig, E. (1870). Ueber die elektrische Erregbarkeit des Grosshirns. Translated by G. von Bonin, In *The Cerebral Cortex*, W.W. Nowinski, ed. (Springfield, IL: Thomas, 1960), p. 73–96.
- Fulton, J.F. (1935). Definition of the motor and premotor areas. *Brain Res.* 58, 311–316.
- Georgopoulos, A.P., Schwartz, A.B., and Kettner, R.E. (1986). Neu-

- ronal population coding of movement direction. *Science* 233, 1416–1419.
- Giszter, S.F., Mussa-Ivaldi, F.A., and Bizzi, E. (1993). Convergent force fields organized in the frog's spinal cord. *J. Neurosci.* 13, 467–491.
- Gottlieb, J.P., Bruce, C.J., and MacAvoy, M.G. (1993). Smooth eye movements elicited by microstimulation in the primate frontal eye field. *J. Neurophysiol.* 69, 786–799.
- Graziano, M.S.A., and Gandhi, S. (2000). Location of the polysensory zone in the precentral gyrus of anesthetized monkeys. *Exp. Brain Res.* 135, 259–266.
- Graziano, M.S.A., Hu, X., and Gross, C.G. (1997). Visuospatial properties of ventral premotor cortex. *J. Neurophysiol.* 77, 2268–2292.
- Graziano, M.S.A., Reiss, L.A.J., and Gross, C.G. (1999). A neuronal representation of the location of nearby sounds. *Nature* 397, 428–430.
- Hoebel, B.G. (1969). Feeding and self-stimulation. *Ann. NY Acad. Sci.* 157, 758–778.
- Huntley, G.W., and Jones, E.G. (1991). Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: a correlative anatomic and physiological study. *J. Neurophysiol.* 66, 390–413.
- Kakei, S., Hoffman, D., and Strick, P. (1999). Muscle and movement representations in the primary motor cortex. *Science* 285, 2136–2139.
- Kennedy, H., Dehay, C., and Bullier, J. (1986). Organization of the callosal connections of visual areas V1 and V2 in the macaque monkey. *J. Comp. Neurol.* 247, 398–415.
- Kurata, K. (1989). Distribution of neurons with set- and movement-related activity before hand and foot movements in the premotor cortex of rhesus monkeys. *Exp. Brain Res.* 77, 245–256.
- Lemon, R.N., and Porter, R. (1976). Afferent input to movement-related precentral neurones in conscious monkeys. *Proc. R. Soc. Lond. B. Biol. Sci.* 194, 313–339.
- Maier, M.A., Armond, J., Kirkwood, P.A., Yang, H.-W., Davis, J.N., and Lemon, R.N. (2002). Differences in the corticospinal projection from primary motor cortex and supplementary motor area to macaque upper limb motoneurons: an anatomical and electrophysiological study. *Cereb. Cortex* 12, 281–296.
- Moran, D.W., and Schwartz, A.B. (2000). One motor cortex, two different views. *Nat. Neurosci.* 3, 963.
- Morasso, P. (1981). Spatial control of arm movements. *Exp. Brain Res.* 42, 223–227.
- Okada, E., Aou, S., Takaki, A., Oomura, Y., and Hori, T. (1991). Electrical stimulation of male monkey's midbrain elicits components of sexual behavior. *Physiol. Behav.* 50, 229–236.
- Penfield, W., and Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 60, 389–443.
- Preuss, T.M., Stepniewska, I., and Kaas, J.H. (1996). Movement representation in the dorsal and ventral premotor areas of owl monkeys: a microstimulation study. *J. Comp. Neurol.* 371, 649–676.
- Quaade, F., Vaernet, K., and Larsson, S. (1974). Sterotaxic stimulation and electrocoagulation of the lateral hypothalamus in obese humans. *Acta Neurochirurgica* 30, 111–117.
- Reina, G.A., Moran, D.W., and Schwartz, A.B. (2001). On the relationship between joint angular velocity and motor cortical discharge during reaching. *J. Neurophysiol.* 85, 2576–2589.
- Rizzolatti, G., Scandolara, C., Matelli, M., and Gentilucci, M. (1981). Afferent properties of periarculate neurons in macaque monkeys. II. Visual responses. *Beh. Brain Res.* 2, 147–163.
- Rizzolatti, G., Camarda, R., Fogassi, L., Gentilucci, M., Luppino, G., and Matelli, M. (1988). Functional organization of inferior area 6 in the macaque monkey. II. Area F5 and the control of distal movements. *Exp. Brain Res.* 71, 491–507.
- Robinson, D.A. (1972). Eye movements evoked by collicular stimulation in the alert monkey. *Vision Res.* 12, 1795–1808.
- Robinson, D.A., and Fuchs, A.F. (1969). Eye movements evoked by stimulation of the frontal eye fields. *J. Neurophysiol.* 32, 637–648.
- Romo, R., Hernandez, A., Zainos, A., and Salinas, E. (1998). Somatosensory discrimination based on cortical microstimulation. *Nature* 392, 387–390.
- Russo, G.S., and Bruce, C.J. (2000). Supplementary eye field: representation of saccades and relationship between neuronal response fields and elicited eye movements. *J. Neurophys.* 84, 2605–2620.
- Salzman, C.D., Britten, K.H., and Newsome, W.T. (1990). Cortical microstimulation influences perceptual judgements of motion direction. *Nature* 346, 174–177.
- Sanes, J.N., Donoghue, J.P., Thangaraj, V., Edelman, R.R., and Warach, S. (1995). Shared neural substrates controlling hand movements in human motor cortex. *Science* 268, 1775–1777.
- Sato, K.C., and Tanji, J. (1989). Digit-muscle responses evoked from multiple intracortical foci in monkey precentral motor cortex. *J. Neurophysiol.* 62, 959–970.
- Schieber, M.H., and Hibbard, L.S. (1993). How somatotopic is the motor cortex hand area? *Science* 261, 489–492.
- Schiller, P.H., and Stryker, M. (1972). Single-unit recording and stimulation in superior colliculus of the alert rhesus monkey. *J. Neurophysiol.* 35, 915–924.
- Scott, S.H. (2000). Reply to “one motor cortex, two different views.” *Nat. Neurosci.* 3, 964–965.
- Sessle, B.J., and Wiesendanger, M. (1982). Structural and functional definition of the motor cortex in the monkey (*Macaca fascicularis*). *J. Physiol.* 323, 245–265.
- Stanford, T.R., Freedman, E.G., and Sparks, D.L. (1996). Site and parameters of microstimulation: evidence for independent effects on the properties of saccades evoked from the primate superior colliculus. *J. Neurophysiol.* 76, 3360–3381.
- Strick, P.L., and Preston, J.B. (1978). Multiple representation in the primate motor cortex. *Brain Res.* 154, 366–370.
- Tehovnik, E.J. (1995). The dorsomedial frontal cortex: eye and forelimb fields. *Behav. Brain Res.* 67, 147–163.
- Tehovnik, E.J. (1996). Electrical stimulation of neural tissue to evoke behavioral responses. *J. Neurosci. Methods.* 65, 1–17.
- Tehovnik, E.J., and Lee, K. (1993). The dorsomedial frontal cortex of the rhesus monkey: topographic representation of saccades evoked by electrical stimulation. *Exp. Brain Res.* 96, 430–442.
- Thier, P., and Andersen, R.A. (1998). Electrical microstimulation distinguishes distinct saccade-related areas in the posterior parietal cortex. *J. Neurophysiol.* 80, 1713–1735.
- Todorov, E. (2000). Direct cortical control of muscle activation in voluntary arm movements: a model. *Nat. Neurosci.* 3, 391–398.
- Weinrich, M., and Wise, S.P. (1982). The premotor cortex of the monkey. *J. Neurosci.* 2, 1329–1345.
- Woolsey, C.N., Settlage, P.H., Meyer, D.R., Sencer, W., Hamuy, T.P., and Travis, A.M. (1952). Pattern of localization in precentral and “supplementary” motor areas and their relation to the concept of a premotor area. In *Association for Research in Nervous and Mental Disease, Volume 30* (New York: Raven Press), pp. 238–264.
- Wu, C.W., Bichot, N.P., and Kaas, J.H. (2000). Converging evidence from microstimulation, architecture, and connections for multiple motor areas in the frontal and cingulate cortex of prosimian primates. *J. Comp. Neurol.* 423, 140–177.